TWENTY-FIRST CENTURY CURES: EXAMINING THE ROLE OF INCENTIVES IN ADVANCING TREATMENTS AND CURES FOR PATIENTS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

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WEDNESDAY, JUNE 11, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10 a.m., in room 2322 of the Rayburn House Office Building, Hon. Joe Pitts (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Shimkus, Murphy, Blackburn, Gingrey, McMorris Rodgers, Lance, Cassidy, Guthrie, Griffith, Bilirakis, Ellmers, Upton (ex officio), Pallone, Engel, Schakowsky, Matheson, Green, Barrow, Christensen, Castor, DeGette, and Waxman (ex officio).

Staff present: Clay Alspach, Chief Counsel, Health; Gary Andres, Staff Director; Matt Bravo, Professional Staff Member; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Brad Grantz, Policy Coordinator, Oversight and Investigations; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Krista Rosenthall, Counsel to Chairman Emeritus; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Tom Wilbur, Digital Media Advisor; Ziky Ababiya, Democratic Staff Assistant; Eric Flamm, Democratic FDA Detailee; Karen Nelson, Democratic Deputy Committee Staff Director for Health; and Rachel Sher, Democratic Senior Counsel.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The chair will recognize himself for an opening statement.

Today's hearing provides us with an opportunity to examine an important aspect of the 21st Century Cures Initiative: whether current economic and regulatory incentives are sufficient to encourage robust investment in the research and development of innovative new drugs and medical technologies.

I am particularly interested in better understanding what we can do to make it more attractive for companies and venture capitalists to invest in the development of therapies that would provide hope

to patients without adequate treatment options. After all, as we have learned, there are only effective treatments for 500 of the 7,000 known diseases impacting patients today.

To help close this innovation gap, as part of 21st Century Cures Initiative, we must take a fresh look at the challenges facing innovative companies and make certain the right incentives are in place so America is home to the next generation of cures.

The Hatch-Waxman Act created the modern generic drug industry as we know it and has brought great benefits to our Nation's patients and health care system. Nonetheless, as Senator Hatch recently explained, since the early 1980s, "the cost of developing a drug has doubled, as has the number of clinical trials necessary to file a new drug application. Further, the number of participants required for those trials has tripled."

We continue to hear about the many unique challenges of developing and testing therapies for patients with rare diseases and certain types of cancer. However, we cannot lose sight of the fact that new products targeting diseases that impact large patient populations such as diabetes and Alzheimer's take much longer to get to market and are therefore becoming less attractive for investors and companies to pursue. Innovative trial designs with surrogate endpoints are almost unheard of in some of these areas, despite the fact that patients and our health care system would greatly benefit from new treatments. If and when they ultimately get to the market, these products are often left with the least amount of patent life and are granted the shortest exclusivity periods. We must reexamine the incentive structure, particularly for small-molecule drugs, before we are left wondering who will be developing the next generation of treatments and in which country.

Finally, for a variety of what are oftentimes different reasons, investment in new medical technology companies is at startlingly low levels. There are only 11 venture capital firms remaining in this space, down from almost 40 in in 2007. In 2013, we witnessed the lowest level of initial funding activity in more than two decades. This is not only a cures issues; this is a jobs issue and one we must address head on.

I want to welcome our witnesses today and look forward to learning more about the incentives necessary to encourage vital investment in biomedical innovation across the board.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

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I want to welcome our witnesses today and look forward to learning more about the incentives necessary to encourage vital investment in biomedical innovation across the board.

Thank you, and I yield the remainder of my time to _____.

Mr. PITTS. Thank you, and I yield the remainder of my time to the vice chairman of the subcommittee, Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman, and I want to join you in welcoming our panel of witnesses. I certainly look forward to hearing your testimony today.

Once again, we are examining the role of various market incentives on the development of new drugs, biologics and devices. From bench to bedside, the timeline right now is about 12 years, and that is a long time. Of all the drugs that enter pre-clinical testing, only five of 5,000 will make it to human testing. Balancing the importance of facilitating innovation and expediting patient access has been a priority of this committee. Many of these incentives have been actually quite successful over the years. Hatch-Waxman—we have a robust market. The Orphan Drug Act—we have encouraged manufacturers to develop and test existing products for the treatment of rare diseases. The bottom line in each instance, patients have benefited.

The greatest market incentive is a developer knowing that there is a market for their product and that it will be covered. Whether the payer is the Federal Government or the private insurance, payers need to know what is coming down the road so that they are prepared to integrate the new treatments into their coverage because really, what difference does it make to the patient that a product was developed if they have got no access to it.

Really, the headline in all of this should be, we have the ability to develop cures that no generation of doctors has been able to deliver to patients ever, and we can't let the regulatory side get in the way. We want to be facilitators. We want to be catalysts.

And again, we thank you for being here. We welcome your testimony this morning, and I yield back.

Mr. PITTS. The chair thanks the gentleman and now recognize the ranking member of the subcommittee, Mr. Pallone, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts.

When we talk about medicines and disease, there is a natural emotion that comes from the personal stories we hear from our constituents as well as from our own lives, and many of us know all too well about the pain and suffering families face when battling an illness and losing those we love.

As Members of Congress, we typically speak about treating disease in sound bites. Innovation, cures, discovery, incentives and, of course, access are some of the key words that we use. In today's hearing, we will hear about the thousands of diseases with little or no treatments and we will examine whether additional steps need to be taken to accelerate biomedical discoveries in this country.

Innovative new drugs for decades have made major contributions to our lives. In many instances, they have allowed us to watch our loved ones get better and live longer, sometimes even healthier lives, and now we are even seeing some new drugs curing diseases outright, discoveries certainly worthy of praise.

But we must be careful in this debate. We can't look at these issues filled with emotion and we certainly can't look at these issues in a vacuum. It is complicated with far-reaching effects, and we continue to battle thousands of rare diseases affecting small populations for which there are no known causes or cures. We need to address this problem. The Orphan Drug Act, which includes tax incentives and market exclusivity, has been successful, leading to a number of medical treatments, and many of these treatments, while they can be expensive, serve a fairly small number of patients.

When we think about diseases like Alzheimer's or chronic conditions like diabetes, we may be talking about treating millions of people for decades, and what is more, baby boomers are aging into Medicare at a pace of thousands a day, so we absolutely need to encourage innovation and help to ensure that new treatments emerge but we also need to make sure that patients have access to affordable treatments. Otherwise we will bankrupt families for which new medicines may be the difference between life and death. And we will strain our federal health care system. Cures and cutting-edge medicines are of no value if their high costs put them out of reach of the patients who need them.

Thirty years ago, Congress sought to address the high costs and access to medicine, and as a result, the Hatch-Waxman Act was negotiated to strike an important balance between providing incentives to innovative new and better medicines and access to lower-cost medicines. Since then, there has been a tremendous public health and economic benefit. Today, generic drugs account for 84 percent of all prescriptions in the United States with savings

amounting to $217 billion annually. But Hatch-Waxman isn't just about lower-cost drugs. Fundamentally, I believe its existence has resulted in competition, innovation, and great discoveries. Without the threat of generic alternatives, brand companies would have little reason to engage in research on new drugs to outpace their competitors. Furthermore, there are real examples of brand companies spurring innovation amongst other brands.

So as we move forward, it is important that we do not alter the central construct of Hatch-Waxman. However, that doesn't mean there aren't additional ways to find further balance in our development ecosystem. In 2012, the committee worked to pass the FDA Safety and Innovation Act, or FDASIA, which included a number of additional economic incentives. One example was the GAIN Act for antibiotics for serious or life-threatening infections. In that provision, we carefully constructed narrowly focused incentives for companies to advance in the antibiotic space. At only 2 years old, there is promise with nearly 17 applications in the pipeline and one approval so far.

So Mr. Chairman, I believe that there are many factors to encouraging and ensuring robust investment in medicines. Federal funding is one notable example. It is the foundation of our biomedical ecosystem and is one of the best investments we can make to spur economic prosperity, drug and device development and cures for the 21st century.

And I would like to yield the remainder of my time, Mr. Chairman, to Ms. DeGette, a member of the full committee who joins us today.

Ms. DEGETTE. Thank you very much. I appreciate you yielding, and I am very proud to be co-chairing the 21st Cures Initiative with Chairman Upton.

This is our second hearing focused on the initiative. The first hearing broadly touched on the eight recommendations provided in the President's Council of Advisors on Science and Technology report on propelling innovation and drug discovery development and education. The hearing today focuses on one of those recommendations, studying current and potential economic incentives to promote drug innovation.

We know there are many types of incentives in place right now—some of the other members have mentioned them—to help spur research and development in both the drug and device space. These range from funding for research and public-private partnerships to tax credits and various exclusivity periods.

I look forward to hearing form the witnesses talking about some of these incentives. For example, the recently implemented exclusivity provided under the GAIN Act seems to be spurring investment in antimicrobial and antifungal drugs. And so there are other initiatives too.

I want to thank you, Mr. Chairman, for having this hearing and I look forward to this continuing discussion that we are having.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the chairman of the full committee, Mr. Upton, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Thank you, Mr. Chairman.

We did launch the 21st Century Cures Initiative with the goal of accelerating the discovery, development, and delivery of innovative new treatments and cures to patients, ensuring that the United States remains the biomedical innovation capital of the world. 21st Century Cures aims to close any gaps between the science of cures and how we regulate those therapies, and this must be an ongoing conversation.

Today we are going to hear testimony about whether our current legislative and regulatory framework encourages innovators to pursue the development of drugs and devices that are crucial to helping our Nation's patients. I am so proud of the fact that this committee recently came together on a bipartisan basis to address this innovation gap in the context of antibiotics, but it is clear that our work is far from over.

We lack effective treatments for almost 95 percent of the known diseases affecting patients today and over 95 percent of drugs in development do not make it to market. In addition to working with the FDA and others to decrease the time and cost it takes to bring new products to patients, we have got to heed the advice of the President's Council of Advisors and take a fresh look at current and potential economic incentives to promote innovation. As we have seen in the context of orphan diseases and most recently for antibiotics, periods of market exclusivity are powerful tools for us to consider in ushering in the next generation of treatments and cures. This is certainly a balancing act, and I am committed to pursuing any such changes only after engaging in a thorough and thoughtful dialogue with all interested stakeholders, which is precisely why we are here today.

The Hatch-Waxman Act is an enduring piece of legislation that will undoubtedly form the basis for any such conversation. I agree with Senator Hatch, who recently said, "The foundation laid by Hatch-Waxman Act 30 years ago will continue to be the mechanism by which the management incentives development of lifesaving drugs but we do have an obligation to periodically reevaluate how the balance can be adjusted to account for the sweeping changes in the broader health care sector."

The time and cost of bringing an innovative product to market today is much different than it was in 1984, and yet under Hatch-Waxman, the same baseline exclusivity period is still granted to new drugs. We have an opportunity today to assess whether we still have the right balance in place, particularly for products meeting unmet medical needs.

We also have an opportunity to hear about incentives for new devices. This committee has worked with FDA and stakeholders to help make the regulation of devices more predictable and consistent, but it is clear that we have to continue that collaboration to not only improve FDA but also coverage and reimbursement.

So I want to thank everyone that is here. Please continue to share your ideas with cures@mail.house.gov. Working together, we are going to make a difference.

I yield the balance of my time to the vice chair of the committee, Ms. Blackburn.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

We launched the 21st Century Cures initiative with the goal of accelerating the discovery, development, and delivery of innovative new treatments and cures to patients, ensuring that the United States remains the biomedical innovation capital of the world. Twenty-First Century Cures aims to close any gaps between the science of cures and how we regulate those therapies. This must be an ongoing conversation.

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We also have an opportunity to hear about incentives for new devices. This committee has worked with FDA and stakeholders to help make the regulation of devices more predictable and consistent, but it is clear that we must continue our collaboration to not only improve FDA but also coverage and reimbursement.

In closing, I want to thank those folks who have responded to our call for input in this 21st Century Cures initiative—we appreciate the thoughtful contributions, especially the responses from everyday Americans. Please continue to share your ideas with cures@mail.house.gov. Working together, we will make a difference.

Mrs. BLACKBURN. Thank you, and I appreciate that we are having this hearing today and focusing on 21st century cures.

The United States has done so much to advance health and wellness in the country. Just looking back over some of the recent accomplishments, in children, 90 percent of all leukemia is cured. You have survival rates for melanoma post 5 years that have doubled. Kalydeco for cystic fibrosis. Diabetes—they have done away with the twice-daily shots. You have got the pump. Now they are working on the artificial pancreas. The list could go on and on talking about different vaccines, but I have to tell you, I am very concerned because when you look at the investment that has taken place in medical devices from 2007 to 2013, it is down 40 percent. This isn't good for us and we want to make sure that the incentive is there to come back into that marketplace just as the chairman

and Ms. DeGette have both mentioned. We have got to reverse that trend for 21st century cures.

Some of the incentives, the protection of intellectual property, the use of new pathways in order to move through the maze of FDA regulation and of course FDASIA has the breakthrough therapy designation, clarity around reimbursement issues that focuses on the value of treatment. These incentives provide an investment in our Nation's fiscal future as well.

Alzheimer's disease is a great example of this. It is one where I have a particular interest and focus. It is something that costs our Nation $215 billion a year. That is about $50,000 per patient, or the median household income, to care for an Alzheimer's patient.

So to focus on these cures is an imperative. It is the proper use of our time. I welcome you and I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the ranking member of the full committee, Mr. Waxman, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman.

This hearing today has very real implications for patients everywhere. How do we ensure that drug and device companies have the right incentives to discover important new treatments for disease? We cannot legislate scientific advances. In some areas, the lack of new treatments is attributable to a lack of scientific knowledge, not the lack of incentives. To tackle these problems, we will need more investment in research.

That is why our country has been so far ahead of the rest of the world. Our taxpayers want basic research to be funded through the National Institutes of Health, and I would assume everybody that cares about this problem is outraged when we see cuts at the NIH budget. But in other areas, incentives can play a key role in sparking and sustaining innovation. That is why it is important for us to consider how the incentives that exist today are working and whether they can be improved.

The good news is that innovation in this country is flourishing. More important new drugs are launched here than any place else in the world. A key reason is that our system recognizes that both competition and market exclusivity can spur innovation. We have led the world in developing new treatments because we have sought to get the balance right.

There are a variety of types of incentives: tax credits, monetary prizes, and public funding of basic scientific research, to name a few. I hope we will focus today on this wide range of incentives. I suspect, however, that much of our time will be spent on patents and marketing exclusivities.

Let me say a few words about these tools because I don't think anyone in Congress has worked longer or harder on getting their use right than I have. I authored the Orphan Drug Act, which provides 7 years' exclusivity to incentivize development of drugs for rare diseases. The 7 years was justified because the small populations in need of these drugs did not provide an adequate market.

The Act has been a resounding success. Prior to enactment, only ten drugs for rare diseases had been developed. In the 30-plus years since enactment, over 400 have been approved and many are in the development stage and are being used without the final approval.

I was the co-author of the Hatch-Waxman law, which established our generic drug system. The Act struck a balance between generic competition and maintaining adequate incentives for brand companies to continue to innovate. We allowed generics to rely on the brands' safety and effectiveness data in order to avoid wasteful duplicative clinical trials. In exchange, we gave the brands 5 years of exclusivity to store some of the patent time lost during the FDA review process. The law has been an enormous success. Today, over 86 percent of prescriptions are generics, yet spending on generics accounts for only 29 percent of total drug spending, and at the same time, the brand industry is booming.

Most people understand that the introduction of generic competition has drastically lowered our national drug bill. But generic competition also has another critical effect that may seem counterintuitive: it also spurs innovation. An innovator company that knows generic competition is just around the bend needs to develop new products. In contrast, excessive periods of exclusivity allow innovators to sit back and relax. Why spend a lot of money on discovering the next groundbreaking product, if it can continue to charge monopoly prices for 10, 12, or even 15 years on a drug that has already been approved? Too much exclusivity is as bad as too little, if not worse. Innovation is stifled by the lack of competition, and American patients foot the bill by paying higher prices for their drugs.

When our committee considers these issues, the first question should be whether new or additional incentives are really needed in any particular area and what is an appropriate incentive. We should insist on getting the answers that are supported with data demonstrating this need. If new marketing protections are warranted, they should be narrowly focused to achieve a targeted aim. Otherwise we run the risk of allowing companies to reap huge windfall profits, windfalls that are paid for by American patients and the government and insurance companies in this Nation.

So I urge caution when considering patents and exclusivity as incentives. These are not the only tools, and in many cases, they are not the best ones for ensuring the development of new cures.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman. The written opening statements of all members will be made a part of the record.

That concludes our opening statements by the members. We will now go to our witnesses. We have one panel with seven witnesses. I will introduce them in the order of their speaking.

First is Mr. Marc Boutin, Executive Vice President and Chief Operating Officer of National Health Council. Then Dr. Sam Gandy, Chair, Mount Sinai Alzheimer's Disease Research Center on behalf of Dr. Ken Davis, the President and CEO of Mount Sinai Health System. Then Mr. Alexis Borisy, Partner, Third Rock Ventures; Mr. Mike Carusi, General Partner, Advance Technology Ventures on behalf of National Venture Capital Association; Dr. Steven Miller,

Vice President and Chief Medical Officer, Express Scripts Holding Company; Dr. Fred Ledley, Professor, National and Applied Sciences, Management Director, Center for Integration of Science and University, Bentley University; and finally, Mr. Scott Hemphill, Professor of Law, Columbia Law School.

Thank you all for coming. You will each have 5 minutes to summarize your testimony. Your written testimony will be made a part of the record. There is a little system of lights on your desk so you have 5 minutes when the green light will be on. When the red light goes on, we ask that you wrap up your opening statement.

So at this time, Mr. Boutin, we will start with you. You are recognized for 5 minutes for an opening statement.

STATEMENTS OF MARC BOUTIN, EXECUTIVE VICE PRESIDENT AND CHIEF OPERATING OFFICER, NATIONAL HEALTH COUNCIL; DR. SAM GANDY, CHAIR, MOUNT SINAI ALZHEIMER'S RESEARCH CENTER, ON BEHALF OF DR. KENNETH DAVIS, PRESIDENT AND CEO, MOUNT SINAI HEALTH SYSTEM; ALEXIS BORISY, PARTNER, THIRD ROCK VENTURES; MIKE CARUSI, GENERAL PARTNER, ADVANCED TECHNOLOGY VENTURES, ON BEHALF OF THE NATIONAL VENTURE CAPITAL ASSOCIATION; DR. STEVEN MILLER, SENIOR VICE PRESIDENT AND CHIEF MEDICAL OFFICER, EXPRESS SCRIPTS HOLDING COMPANY; DR. FRED LEDLEY, PROFESSOR, NATURAL AND APPLIED SCIENCES, AND MANAGEMENT DIRECTOR, CENTER FOR INTEGRATION OF SCIENCE AND INDUSTRY, BENTLEY UNIVERSITY; AND C. SCOTT HEMPHILL, PROFESSOR OF LAW, COLUMBIA LAW SCHOOL

STATEMENT OF MARC BOUTIN

Mr. BOUTIN. Good morning, Chairman Pitts, Ranking Member Pallone, Ms. DeGette, members of this subcommittee.

There are more than 133 million people living with one or more chronic conditions. That is more than 40 percent of the population. Effective treatments are available for some but for many patients, all they have is hope.

My name is Marc Boutin. I am the Executive Vice President and Chief Operating Officer at the National Health Council. We provide a united voice for people with chronic disease and disabilities.

As a child, I remember growing up in a tiny town in northern Maine. Every surface of my home was covered in floral wallpaper, including the light switches. You actually had to rub the wall to find the switch. The wallpaper, the rugs, the furniture, everything was covered in flowers, and when my mom sat perfectly still in her floral dress, you couldn't see her. In my 30s, I remember sitting in the doctor's office when my father was told he had incurable cancer. My mom became his primary caregiver even though she had multiple chronic conditions herself. I held my father's hand when he took his final breath. My mom soon died on my birthday. Dismantling our family home was difficult. All the memories, all that wallpaper. Getting the house ready to sell was not easy but it had to be done.

Nearly every person in this room has been touched by the burden of disease. Michael Gollin sitting behind me is an intellectual-property lawyer. He is also living with ALS, or Lou Gehrig's disease,

which progressively robs you of your ability to walk, talk, swallow and even breathe.

Thirty years ago, Representative Waxman coauthored the Hatch-Waxman Act, which updated our innovation ecosystem and made medications affordable for millions of Americans. But as Senator Hatch recently wrote, "We cannot rest on our laurels. We have an obligation to periodically reevaluate and adjust to account for the sweeping changes in the health sector."

Our current innovation ecosystem was built decades ago, long before we mapped the human genome, had supercomputers or advanced diagnostics. Much like my family home, the ecosystem has not kept pace with time. No one is to blame for this. It just happens. You get used to the wallpaper.

The 21st Century Cures Call to Action provides an opportunity to update, to modernize. While we may not all yet agree on the specific solutions, consensus is emerging on some of our most pressing challenges. Let me address two.

First, we all know that you need a patent to develop a new medicine but just because you cure Parkinson's or lupus doesn't mean you get a patent. Some of the best science is not translated into treatments simply because they don't meet the technical requirements of the law. From a patient perspective, this makes no sense, and Congress can fix it.

Second, our current system encourages the fastest, least expensive innovation, not necessarily the treatments that are most important to society or individual patients. As you know, patents run concurrently with clinical and regulatory review. As a result, the best and most promising medicines sometimes receive the shortest protection from general competition. For example, conditions which progress slowly like Alzheimer's can come to the market with the shortest periods of protection. This also encourages the development of treatments for late-stage illness rather than early-stage illness despite the huge social and economic value of addressing and preventing disease early. From a patient perspective, this makes no sense, and Congress can address it.

The MODDERN Cures Act, introduced by Representative Lance with bipartisan support, is the first legislative attempt to address these two challenges. It promotes the best science, not the best patent, but only for drugs that address an unmet medical need.

On behalf of my dad, my mom, Mr. Gollin and nearly everyone in this room affected by disease, thank you for including the patient community in this multi-stakeholder approach. We stand willing, ready and able to help you solve this and other complex challenges. It is time to take down the wallpaper. It is time to modernize our innovation ecosystem. Thank you.

[The prepared statement of Mr. Boutin follows:]

Testimony of Marc Boutin, JD, Executive Vice President and Chief Operating Officer of the National Health Council

21st Century Cures Initiative Hearing - June 11, 2014

House Committee on Energy and Commerce

June 9, 2014

Summary

More than 133 million Americans – over 40% of the U.S. population – live with a long-term disease or disability.[1] For many of them there are no treatments, and for a large percentage of people whose conditions have treatments, the current treatments do not work.[2] To address these unmet medical needs, we need to ensure that economic incentives and policies encourage the development of the most promising therapies.

Two major barriers currently prevent promising medicines from being developed or reaching patients: (1) a complete lack of patent protection, and (2) the lack of a predictable post-approval period of patent protection. The primary determinant of whether a product is developed should be its social utility, not the strength of its patent protection. Unfortunately, this is not currently the case, and if a medicine fails this patent protection assessment, it is routinely abandoned and left dormant.

H.R. 3116, the Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act of 2013, or MODDERN Cures Act, was drafted to remove these barriers and align economic incentives with the needs of patients by setting a term of regulatory exclusivity for the development of new drugs intended to treat unmet medical needs. For a promising product with no or uncertain patent protection, the MODDERN Cures Act would protect the medicine from generic competition for a specific period of time after FDA approval, thereby eliminating the question of whether a medicine will have sufficient patent protection from the development equation. In addition, the MODDERN Cures Act promotes increased data transparency.

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[1] CDC Website, available at: http://www.cdc.gov/chronicdisease/overview/index.htm (last accessed June 5, 2014).
[2] Spear et al. Clinical application of pharmacogenetics, *Trends Mol Med* (2001) 7(5):201-4.

Introduction

The National Health Council (NHC) welcomes the opportunity to submit the following testimony to the House Committee on Energy and Commerce to explain the need to remove existing barriers to the development of promising treatments for unmet medical needs. The NHC is the only organization that brings together all segments of the health community to provide a united voice for the more than 133 million people with chronic diseases and disabilities as well as their family caregivers. Made up of more than 100 national health-related organizations and businesses, its core membership includes the nation's leading patient advocacy groups, which control its governance. Other members include professional societies and membership associations, nonprofit organizations with an interest in health, and major pharmaceutical, medical device, biotechnology, and insurance companies.

The magnitude of patient need is great. More than 133 million Americans – over 40% of the U.S. population – live with a chronic disease or disability.[3] But for many people there are no treatments, and existing treatments work for only 50-75% of the patients who currently use them.[4] There are limited treatment options for too many diseases and disabilities, including mental health aliments, neurological, autoimmune and many rare diseases, or for the prevention of various diseases and disabilities. Millions of patients struggle daily with conditions such as Alpha-1, ALS, Alzheimer's, epilepsy, lupus, mesothelioma, and multiple sclerosis. Many are waiting for a single treatment, while others wait for new and better medicines.

I am honored to mention one patient with a chronic condition – Michael Gollin. Mr. Gollin is a patent attorney. He also lives with ALS, commonly known as Lou Gehring's Disease.

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[3] CDC Website, available at: http://www.cdc.gov/chronicdisease/overview/index.htm (last accessed June 5, 2014).
[4] Spear et al. Clinical application of pharmacogenetics, *Trends Mol Med* (2001) 7(5):201-4.

Patients like Mr. Gollin should not lose out on potentially life-saving treatments because our current system fails to address barriers to the development of new treatments.

Current policies have not kept pace with the evolution of science in the U.S. As Senator Hatch explained in his recent foreword to the *William Mitchell Law Review* issue on the anniversary of the Hatch-Waxman Act: While "the foundation laid by the Hatch-Waxman Act thirty years ago will continue to be the mechanism by which the government incentivizes development of lifesaving drugs. . .we cannot rest on the laurels of this legislative achievement. . .[W]e have an obligation to periodically reevaluate how the balance can be adjusted to account for the sweeping changes in the broader health care sector."[5]

Insufficient Patent Protection Prevents Promising Medicines from Reaching Patients

Two situations currently prevent some promising medicines from being developed and making it to the market and patients: (1) a complete lack of patent protection, and (2) the lack of a predictable and sufficient period of patent protection once the medicine enters the market.

First, the best new medicines do not automatically qualify for a patent, and without any patent protection, manufacturers will not continue developing the treatments, despite their potential to treat unmet medical needs and benefit patients. In order for any invention to secure a patent, it must be deemed as novel and nonobvious. While these thresholds to receiving a patent are designed to encourage ingenuity, they have also created barriers to innovation in the drug development process.[6]

As for novelty, "a drug cannot be patented if it was previously disclosed to the public; no exception is made for when the disclosed drug has not yet been tested in clinical trials and thus

[5] Hatch, O. William Mitchell Law Review. Accessible at: http://www.wmitchell.edu/lawreview/Volume40/40_IV.html. (last accessed June 7, 2014)

[6] Roin, Benjamin N., Unpatentable Drugs and the Standards of Patentability (February 2009). Texas Law Review, Vol. 87, pp. 503-570, 2009. Available at SSRN: http://ssrn.com/abstract=1127742

has not been approved by the FDA.". Current law allows seemingly insignificant disclosures to undermine the novelty of drugs, which makes it easy for researchers to unwittingly disclose their discoveries. Companies [file] overly broad patent applications to establish priority over large numbers of potential new drugs. As their research advances, the companies typically disclaim most of those compounds from their applications, leaving only the prior disclosure of the drugs. Practices such as these have created a significant body of potentially valuable drugs that cannot be patented."

Nonobviousness is defined as "A new drug with beneficial therapeutic properties is therefore considered obvious if those properties would have been reasonably expected at the time it was invented." Obvious drugs are defined as ones that would have been reasonably expected to succeed at the time of their invention...drugs that initially look most likely to be effective are often the least likely to be patentable." The [nonobviousness] standard withholds patented protection from drugs based on the scientific advances that allowed researchers to identify them as ones that are likely to be effective." Without MODDERN, the scope of the problem caused by the nonobviousness standard is likely to expand as scientific progress increases the likelihood of success for many products, rendering more and more of them "obvious."

Second, the unfortunate reality is that manufacturers stop developing a drug when they believe that its patent protection will not extend long enough after the drug enters the market to allow the company to re-coup their investment. Because drug manufacturers must apply for patents very early in the research and development process, there can be little or no patent life left when the drug finally enters the market, even with patent term extensions granted through Hatch-Waxman. The longer the drug development process goes on, the shorter the patent term once the drug is approved.

This uncertainty discourages companies from pursuing medicines with long development timelines in favor of those with shorter development timelines. In cancer, for example, this leads to more research and development of drugs intended to treat later-stage cancers, which often have shorter development timelines.[7] Conversely, the development of promising drugs intended to prevent cancer or treat early-stage disease with longer development timelines is reduced because of shorter periods of patent protection once the drugs are approved. This leads to increased research and development in the later cancer stages at the expense of the enormous public health benefit of studying drugs to treat early-stage patients or to prevent cancer. Longer development times are also likely for innovative drugs that could treat a disease that has never had any treatments, a drug with a new mechanism of action, or a drug to prevent, cure, or slow the progression of a disease or disability.

How Congress Can Help – the MODDERN Cures Act

I would like to commend Ranking Member Waxman for his courageous efforts to overhaul the pharmaceutical industry with both the Hatch-Waxman Act and the Orphan Drug Act. These laws have made a huge difference in the lives of patients. It is once again time for courageous action. We need to re-align our economic incentives and policies to encourage the development of treatments for people with unmet medical needs.

Patient advocacy organizations have already begun to address the patent protection barriers to developing new treatments by crafting a bill titled H.R. 3116, the Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act of 2013, or the MODDERN Cures Act. The bill was introduced in the House in September 2013 by Representative Leonard Lance and is currently cosponsored by 54 other Members of Congress. I want to recognize and

[7] Budish et al. National Bureau of Economic Research. Do fixed patent terms distort innovation? Evidence from cancer clinical trials. September 5, 2013. Available at: http://www.nber.org/papers/w19430.pdf. (last accessed June 9, 2014)

commend Representative Lance on his leadership and work in moving this bill forward. The MODDERN Cures Act aligns incentives with the needs of patients by setting a term of regulatory exclusivity for medicines intended to treat unmet medical needs. In addition, it encourages the development of innovative diagnostics that help identify which patients will benefit from a specific therapy. The MODDERN Cures Act aims to ensure that the most promising therapies for unmet medical needs are not shelved due to uncertain patent protection.

Specifically, the MODDERN Cures Act provides for a drug or biologic to be designated as a "dormant therapy" if it is a new medicine being studied to treat an unmet medical need. A designated dormant therapy can receive regulatory exclusivity, which protects the drug from generic competition for a certain amount of time after FDA approval. This allows manufacturers to pursue medicines that have the greatest potential to meet an unmet medical need, even if the treatment has no patent protection.

The MODDERN Cures Act also addresses the problem of uncertainty created by long, unpredictable development and review times for treatments that address unmet medical needs.[8] The Act's provisions give manufacturers the certainty that the medicine will be protected from generic competition for a specific period of time once approved, freeing up manufacturers to decide a medicine's fate not by whether enough patent protection may exist at an unknown date in the future, but by the drug's potential to benefit patients and enhance the public's health. We anticipate that this will result in increased research and development into medicines with the potential to prevent disease or disability or treat early-stage conditions.

Finally, the MODDERN Cures Act contains the additional benefit of consistency with the increasing demand that clinical studies data be made public, i.e., a policy of enhanced data

[8] Designation as a dormant therapy is optional. If a product has sufficiently strong patent protection, manufacturers will still able to use the existing provisions in the Hatch-Waxman Act.

transparency. Many anticipate that increased data transparency will benefit patients by helping to eliminate unnecessary and costly duplication of clinical studies, allowing others to confirm or challenge study conclusions, facilitate learning about existing medicines, and help to inform patient decisions on treatment and physician prescribing – all accelerating research and enhancing patient outcomes. Under the MODDERN Cures Act, dormant therapies receive a set term of regulatory exclusivity, which decreases industry reliance on the use of trade secrets to protect their products. Additionally, the MODDERN Cures Act requires that manufacturers waive patent enforcement beyond the period of regulatory exclusivity, thereby creating a predictable timeline for generic manufacturers to bring their products to market. This bill contains the strongest "anti-evergreening" protections ever included in legislation.

Conclusion

The MODDERN Cures Act removes barriers to the development of products that treat unmet medical needs of people with devastating diseases that have few or no current treatments. This can benefit a great number of patients who suffer from a multitude of diseases – from mental health aliments to neurological, autoimmune, and rare diseases.

Congress has recently demonstrated its willingness to legislate needed fixes by enacting certain bill provisions incentivizing innovative diagnostics. These provisions were originally included in the MODDERN Cures Act and were enacted on April 1 of this year as part of the Protecting Access to Medicare Act of 2014. The new law establishes a value-based payment system for diagnostic tests and a process for assignment of a temporary reimbursement code to a new test. I commend Congress for taking this step and strongly urge the Committee's support of the remaining provisions of the MODDERN Cures Act.

All patients, including Mr. Gollin, who continue to wait for new treatments for their unmet medical needs, deserve a modernized regulatory system that incentivizes innovation and helps to bring life-saving therapies to the people who need them. Passing the MODDERN Cures Act of 2013 is a much-needed step to attain the goals of the 21st Century Cures Initiative.

Thank you very much.

Mr. PITTS. The chair thanks the gentleman and now recognizes Dr. Gandy 5 minutes for an opening statement.

STATEMENT OF SAM GANDY

Dr. GANDY. Chairman Pitts, Ranking Member Pallone, distinguished members of the Subcommittee on Health, thank you for inviting me here today. I am Dr. Sam Gandy. I am Professor and Chair of Alzheimer's Disease Research at Mount Sinai Medical Center and Director of the Center for Cognitive Health Care. Dr. Ken Davis was meant to be here addressing you but he became ill at the last minute and was unable to come. Thank you for allowing me to present in his stead.

In the 1970s, as a young researcher, Dr. Davis was the first to show that Alzheimer's symptoms could be improved by restoring levels of a brain chemical called acetylcholine as required for memory function. His work eventually lead to FDA approval of three of the four drugs currently on the U.S. market for Alzheimer's disease but that was decades ago, and incredibly, in terms of caring for Alzheimer's patients, almost nothing has changed.

The need for breakthrough medications for Alzheimer's is greater than ever, and the public health impact and the economic impact of Alzheimer's are both escalating.

Alzheimer's affects more than 5 million American seniors today, and by 2050, that number will rise to 15 million. Fully one-half of everyone over age 85 is demented. That means that everyone across the country and everyone in this room who lives past age 85 will be either a patient or a caregiver.

The financial implications are staggering. This year, Medicare and Medicaid are expected to pay $150 billion in acute, chronic and hospice care for individuals with Alzheimer's. The Medicare cost of caring for Alzheimer's will increase more than 600 percent over the next 35 years, rising to $627 billion.

Alzheimer's symptoms begin when people are in their 70s, so if we were able to slow the progression of the disease by half, most of these individuals would not develop symptoms until their 90s, and indeed, many would not live long enough to develop the disease at all. If we could simply delay the onset of Alzheimer's by 5 years, that would cut costs to all payers by half a trillion dollars by 2050.

Scientific opportunities for breakthrough oral medications, in other words, pills, have never been more promising. An extraordinary series of recent studies have found that most people who will eventually develop Alzheimer's accumulate in their brains clumps of a material known as beta amyloid, and this begins two decades or more before symptoms. My own research career began in the 1980s when my team identified the first model drugs that reduce amyloid buildup.

The FDA appropriately requires that safety and efficacy of new drugs must be demonstrated in two independent and most commonly sequential trials. Developing a drug for Alzheimer's is a slow process. Unlike antibiotic medications, for example, that can be tested over a few weeks, Alzheimer's trials require 3 to 5 years. When that is added to, say, 2 years to recruit patients and another year to analyze the results, virtually all the drug's patent life will

have lapsed. Because of this, many drug companies, I would say most, are reducing their emphasis on Alzheimer's.

As you well know, Congress has stepped in before to provide market incentives for research. We now need an exclusivity policy for orally administered pills that slow Alzheimer's. Why do I stress the need for a pill? Because infused biologics can cost as much as 20 times the cost of ordinary medication. For Alzheimer's, that kind of cost would provide no fiscal advantage.

In conclusion, Alzheimer's science is poised to accelerate but business incentives must be realigned in order to provide for the public's best interest. By providing market exclusivity for pills, we would allow innovators to receive a return on their expenditure of resources. In exchange, we would bend the dementia cost curve and reduce the number of individuals suffering from Alzheimer's disease.

I would like to thank the subcommittee for inviting me here today and for shining a spotlight on this important issue. Thank you.

[The prepared statement of Dr. Gandy follows:]

Energy and Commerce Committee
Subcommittee on Health

"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients"

June 11, 2014 at 10am

Testimony from
Kenneth L. Davis, M.D.
Chief Executive Officer and President
Mount Sinai Health System

Chairman Pitts, Ranking Member Pallone, and distinguished members of the Subcommittee on Health, thank you for inviting me to testify.

My name is Dr. Kenneth Davis and I am here today to testify in an individual capacity.

I am the CEO and President of the Mount Sinai Health System in New York. The Mount Sinai Health System is an integrated health care system encompassing the Icahn School of Medicine at Mount Sinai and seven hospital campuses in the New York metropolitan area, as well as a large regional ambulatory footprint. The Mount Sinai Health System, serving a broad spectrum of patients, is one of the largest health systems in New York State. Mount Sinai is supported by a number of programs, including the Center for Medicare and Medicaid Innovation (CMMI), the Patient-Centered Outcomes Research Institute (PCORI) and the Medicare Shared Savings Program to encourage the change from volume- to value- based care.

By way of background, I was named CEO and President of the Mount Sinai Health System in September 2013 following the inclusion of Continuum Health Partners into our health system. For the decade prior to that, I served as President and CEO of The Mount Sinai Medical

Center which entered a new era of innovation in collaborative research, education, and clinical care. A Professor of Psychiatry and Pharmacology at Icahn School of Medicine at Mount Sinai, I received my bachelor's degree from Yale College and my medical degree from Mount Sinai School of Medicine. I completed an internship, residency, and fellowship in psychiatry, and pharmacology, respectively, at Stanford University Medical Center, and thereafter won a career development award from the Veterans Administration to pursue my research in cholinergic mechanisms and neuropsychiatric diseases.

In 1979, I joined the faculty at Mount Sinai, becoming Chief of Psychiatry at the Bronx Veterans Administration (VA) Medical Center. At that time, I spearheaded Mount Sinai's research program in the biology of schizophrenia and the therapeutics of Alzheimer's disease and directed Mount Sinai's National Institute on Aging (NIA)-supported Alzheimer's disease Research Center from 1984 through 2002. My work focused on all aspects of experimental therapeutics, including animal models, assessment instruments, and design issues in drug testing. As early as 1978, I first suggested that treatment of a particular brain chemical deficiency could be useful for the treatment of Alzheimer's disease, and shortly thereafter I conducted the first positive proof of concept study in this disease using drugs called cholinesterase inhibitors. Early on in Alzheimer's, the cells that produce a chemical called acetylcholine begin to fail, and the levels of this important chemical plummet. The medication helps restore the levels of this chemical so that the nerve cells can resume their usual conversations. Subsequently, I coordinated the first multicenter NIA-funded trial of the first orally active cholinesterase inhibitor known as tacrine. This work eventually led to the discovery, development and approval of the drugs used for Alzheimer's today. Aricept (or donepezil), Exelon (rivastigamine), and Razadyne or Reminyl (galantamine) are names that you might have encountered. Either I, or a member of my staff,

helped to direct Pfizer, Novartis or Johnson & Johnson in the development of these drugs. In 1987 I was appointed Chairman of Psychiatry, Mount Sinai School of Medicine.

I also directed the NIMH funded Silvio O. Conte Center for the Neurosciences of Mental Disorders. This multimillion-dollar Center focuses on schizophrenia and is based on the premise that white matter, oligodendrocytes and myelin may be compromised in schizophrenia. It has opened an entirely new approach to this devastating disease. Over the course of my career, I have received a number of NIH grants to study major brain diseases. In addition, I have authored or co-authored more than 575 scientific articles and I have been recognized by ISI as one of the most highly cited researchers in the field of brain diseases. My wife, Dr. Bonnie Davis, is also researcher and inventor of brain disease therapeutics.

I have had the privilege of serving terms as President of the Society of Biological Psychiatry and the American College of Neuropsychopharmacology, as well as Chairman of the Board for the Greater New York Hospital Association, and the League of Voluntary Hospitals & Homes of New York. In addition to my election to membership in the Institute of Medicine (IOM) of the National Academy of Sciences I was proud to receive the George H.W. Bush Lifetime of Leadership Award—a distinction given to Yale alumni athletes who make significant breakthroughs in their professions, the Rita Hayworth Award from the Alzheimer's Association, the Kempf Fund Award for Research Development in Psychobiological Psychiatry from the American Psychiatric Association, the Gold Medal Award from the Society of Biological Psychiatry for Outstanding Achievement in Psychobiological Research, the American Psychiatric Association Award for Research in Psychiatry, and the Joel Elkes International Award given by ACNP for outstanding research in neuropsycho-pharmacology.

This background hopefully demonstrates my commitment and expertise in the issue before the Committee today. I would like to start by commending the Committee for holding this important hearing to discuss the value of incentivizing drug development. While the solution on how to incentivize drug development may be debated, we all can agree that the problem is pervasive: too many individuals in this country are suffering from chronic conditions without the aid of therapeutics. Not only does this have a harmful impact on families, but we must also remember that the lack of therapeutics for chronic diseases places an enormous strain on our country's finances. Chronic conditions, such as Alzheimer's disease and other dementias, are an enormous part of the cost to our health care system. Without novel therapeutics to prevent or better treat these conditions, costs will only escalate. We must find a better solution than the status quo.

In order to bend the dementia cost curve over the long term, we need laws that are aligned with our nation's priorities and the public good, and those that will encourage the development of orally administered compounds for Alzheimer's disease or other chronic diseases. Specifically, I suggest we offer extended market exclusivity protection for truly innovative compounds that reduce the rate of disease progression. Since the development of cholinesterase inhibitors there has only been one other approved drugs for Alzheimer's (Namenda) and that was over 20 years ago. We need to encourage drug development in order to bring new Alzheimer's drugs to market.

Alzheimer's affects more than five million seniors today and, this year, Medicare and Medicaid are expected to pay $150 billion in health care, long term care and hospice for individuals with

Alzheimer's and other related dementias.[1] By 2050, that number could rise to between 13.8 million and 16 million Americans with Alzheimer's whose care will cost Medicare and Medicaid six times their spending today.[2] According to a recent study, women in their 60s are twice as likely to get the disease as they are to get breast cancer.[3] In 2014, an estimated 700,000 Americans will die with Alzheimer's.[4]

Since the disease kills slowly over a period of 10 years, each individual with Alzheimer's could generate a high cost over the course of his or her illness. This year, the total cost for all individuals with Alzheimer's and other dementias are estimated to be over $200 billion.[5] A 2010 Alzheimer's Association report demonstrated that the cost of caring for individuals with Alzheimer's and other dementias will increase more than 600 percent under Medicare, from $88 billion in 2010 to $627 billion in 2050.[6] In addition, Medicaid costs will increase 400 percent, from $34 billion in 2010 to $178 billion in 2050.[7]

If we are to have any chance of mitigating this epidemic, we must find ways to encourage the development of drugs that slow the progression or delay the onset of the inevitable brain failure that characterizes Alzheimer's. Specifically, we need to find incentives for the development of orally administered compounds that alter the course of the disease. As you well know, Congress has stepped in before to provide market incentives for research (i.e., the Orphan Drug Act and the biologics provision in the Affordable Care Act). We now need a similar exclusivity policy extended narrowly to include orally administered compounds that can slow the Alzheimer's epidemic.

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[1] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, *Alzheimer's & Dementia*, Volume 10, Issue 2, Pages 16 & 43.
[2] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, *Alzheimer's & Dementia*, Volume 10, Issue 2, Page 21 & 52.
[3] Alzheimer's Association Website, Alzheimer's Facts and Figures, http://www.alz.org/alzheimers_disease_facts_and_figures.asp#women. Accessed June 5, 2014.
[4] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, *Alzheimer's & Dementia*, Volume 10, Issue 2, Page 25.
[5] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, *Alzheimer's & Dementia*, Volume 10, Issue 2, Page 43.
[6] Alzheimer's Association, "Changing the Trajectory of Alzheimer's Disease: A National Imperative," 2010. Page 4.
[7] Alzheimer's Association, "Changing the Trajectory of Alzheimer's Disease: A National Imperative," 2010. Page 4.

With the sequencing of the human genome and other biomedical breakthroughs, drugs to address Alzheimer's disease are more possible than ever. An extraordinary serious of recent studies have found that people who eventually develop Alzheimer's begin accumulating clumps of protein known as beta amyloid as long as 25 years before symptoms begin. Thus, we need to develop a drug that will slow this progress in patients before they are symptomatic. If we were to develop a drug that would be given before individuals were symptomatic, that drug would push back the development of the disease, and as a country we would incur much lower rates of Alzheimer's disease.

Most individuals show signs of Alzheimer's in their 70s, so if we were able to slow the progress of the disease by 50 percent, most of these individuals would not show symptoms until their 90s. However, because toxicity must be assessed and because the FDA requires that efficacy must be demonstrated in two independent trials, developing a drug to address Alzheimer's could easily take as long as the patent life on any compound. For example, such studies could require these pre-symptomatic patients to take the experimental drug for 5 years, take an additional two years to enroll an adequate number of patients, and another year to analyze the data. Since the two trials would rarely be done in parallel, the result of the first trial would be needed to justify the huge expenditure of the second trial. Thus, assuming success (which is far from guaranteed), there would be virtually no patent life left and thus no real incentive for a pharmaceutical company to invest the resources and time in this science. And this is the most optimistic example, where patients begin treatment 5 years before onset of symptoms. Since those protein clumps become visible as long as 15 years before symptoms, we may well be headed toward initiation of therapy to people in their mid-50s in order to prevent a disease that would have developed in their 70s.

Interventions being evaluated today include a class of drug known as biologics. These drugs themselves are proteins which means that they are administered by infusion and require refrigeration. As you know, the Affordable Care Act encourages the development of these drugs by providing 12 years of exclusivity, but these drugs are expensive. Biologics may cost as much as 22 times the cost of ordinary drugs and, at that rate, a biological treatment that alters progression of Alzheimer's would be as or more expensive than the cost of treating patients with the disease, and hence will not help to save Medicare from insolvency.[8]

Alzheimer's science is poised to accelerate but drug development policies and incentives must be realigned in order to provide for the public's best interest. Such realignment will inevitably align with the best interest of our health care economy. The 2010 Alzheimer's Association report also showed that if we could introduce a treatment to delay the onset of Alzheimer's by five years, the total costs to all payers would fall by $447 billion in 2050.[9] These are real savings that will have a substantial impact, not only on families but on our nation's fiscal crisis.

Therefore, in order to bend the dementia cost curve, Congress should develop legislation to provide market exclusivity – independent of patent life – for orally administered compounds that attenuate Alzheimer's pathology and slow dementia progression. This narrow approach would allow innovators to receive a return on the expenditure of resources leading to a discovery of a therapeutic to treat Alzheimer's disease. In exchange, with an affordable treatment, we would bend the dementia cost curve and begin to attenuate the exploding cost of caring for Americans suffering from Alzheimer's disease.

[8] Op-ed by Anthony D. So and Samuel L. Katz, "Biologics Boondoggle," *New York Times*, March 7, 2010.
[9] Alzheimer's Association, "Changing the Trajectory of Alzheimer's Disease: A National Imperative," 2010. Page 8.

In conclusion, I would like to again thank this Committee for shining a spotlight on this important issue.

Mr. PITTS. The chair thanks the gentleman and now recognizes Mr. Borisy 5 minutes for an opening statement.

STATEMENT OF ALEXIS BORISY

Mr. BORISY. Good morning, Chairman Pitts, Ranking Member Pallone and members of the subcommittee. My name is Alexis Borisy, and I am a Partner at Third Rock Ventures. At Third Rock, our mission is to create, launch, and grow innovative companies that will make a meaningful difference for patients, for physicians, for our health care system overall. I applaud this committee for initiating the 21st Century Cures Call to Action to ensure that U.S. biopharmaceutical and life sciences industry is best equipped to maintain global leadership and deliver lifesaving medicines.

Successful development of new medicines is dependent on policies that support the entire life sciences ecosystem from the lab to the patient. Disrupting any part of the ecosystem weakens the entire enterprise. This endeavor is high risk, taking over a decade and more than a billion dollars to deliver a single new drug. But there can be no question of the reward. Over the last 20 years, we have provided medicines that have changed and saved the lives of patients with diseases such as cancer, heart disease, HIV/AIDS.

This hearing is focused on a critical component of ensuring a forward-learning biopharmaceutical industry, life sciences industry. What incentives are needed to advance treatments and cures? One key to a robust life sciences industry is a national commitment to support basic research. The United States has long been a world leader in basic research but funding for NIH has been flat or declining for the past several years. Diminished support for basic research will lead to a smaller pipeline of next-generation medicines and impede our country's innovation potential.

Building from that base, venture funding is the lifeblood of small biotech companies. However, early-stage venture investment is under significant pressure in the life sciences. A primary reason for its decline is the increased time and cost of developing new treatments. These struggles are especially acute for drugs designed to treat chronic diseases with larger patient populations. The decision to deploy capital is directly impacted by regulatory and reimbursement behaviors. Better enabling and encouraging FDA to utilize flexible approaches and modern tools would have a positive impact on venture funding.

For example, since the implementation of the accelerated approval pathway, over 80 drugs have been approved, most in cancer and HIV. Likewise, in recent years, FDA has shown an increased willingness to work with companies to develop more effective clinical development programs for rare diseases. The majority of designations under the new breakthrough therapy program are also for cancer and for rare diseases. The time required to put a drug on the market is usually longer than the length of time of a typical venture capital investment fund.

The modern approach to regulation that exists now for cancer and rare diseases attracts investment for three important reasons. First, the regulatory process is more interactive, flexible and reflective of the disease and patient being treated. Second, the amount of investment required to fund a company through proof of concept

is better understood, and third, the next step in the innovation ecosystem, be that a larger company or public investors, feel more confident about the development and approval process going form that step further.

The results are clear. Over a third of recent drugs approved have been drugs for rare diseases, and oncology remains one of the hottest investment areas. However, the same cannot be said for chronic diseases where the regulatory requirements are greater. Without improving these processes, early-stage investment in those areas will continue to struggle. We must ask ourselves how we can learn from rare disease and oncology and work to improve how we treat conditions like obesity, diabetes and Alzheimer's, which have a dramatic impact on our long-term health care costs. We must advance to a system that critically determines whether the information required is actually informative as to the potential use of the drug in the real world. Creating approval pathways that enable the development of drugs for subpopulations of patients in these chronic diseases could be a game changer.

There is also a need to provide incentives for the development of new diagnostics. I applaud Congress for passing PAMA, which includes a provision designed to significantly improve reimbursement for diagnostics but its ultimate impact will be determined by the rule writing process. I would like to recommend that we consider a program for diseases important to the public health with high unmet dg needs where we could identify these diseases critical to the Nation's health and establish a payment policy for these desired diagnostics. Clear reimbursement policies for personalized-medicine tools combined with modern regulatory approaches would advance personalized medicine by leaps and bounds.

Congress has the opportunity to support a policy environment that fosters the search for the next generation of cures and treatments, and I applaud the committee for taking steps to improve this process.

Thank you for the opportunity to share my thoughts.

[The prepared statement of Mr. Borisy follows:]

Testimony of Alexis Borisy
Partner, Third Rock Ventures
Before the U.S. House of Representatives
Energy and Commerce Subcommittee on Health Hearing

"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients"

June 11, 2014

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, my name is Alexis Borisy, and I am a partner at Third Rock Ventures. Our firm's mission is to launch and grow exceptional healthcare companies. Our work focuses on forming and building innovative companies in areas of disruptive sciences and medicines. We work to advance pipelines to the clinic and develop new products that will make a meaningful difference for patients, physicians, and our healthcare system overall. I personally have over 20 years of experience in building and operating innovative science-based companies. In addition to my role as a Partner with Third Rock, I am Chairman of the Board and co-founder of NASDAQ-listed Foundation Medicine, Chairman of Warp Drive Bio, CEO for Blueprint Medicines, and serve on the Boards of the National Venture Capital Association and the Biotechnology Industry Organization.

I applaud this Committee for initiating the 21st Century Cures Call to Action and its commitment to finding solutions that will ensure the United States biopharmaceutical industry is best equipped to maintain global leadership and empowered to deliver the next generation of medicines. Our understanding of diseases and how we develop medicines has advanced tremendously over the last 20 years. With over 3,400 medicines in development and over 2,000 public and private companies in the U.S., the promise of this industry is great.[1,2] We have the potential to transform how we treat patients with life-threatening and chronic diseases, a goal that not only would improve the lives of patients and their families but create new solutions to our nation's most pressing health care needs.

This hearing is focused on a critical component of ensuring a forward-leaning and robust biopharmaceutical industry – what incentives are needed to advance treatment and cures? Before I discuss specific policies and offer ideas for consideration, it is important to understand that successful development of new medicines is dependent on policies that support the entire life science ecosystem – beginning with basic research and ending with providing treatments and therapies to patients. Disruption or weakening of policies that negatively impact any part of this ecosystem weakens the entire enterprise.

Assuming that a strong foundation of societal investment in basic research exits, then developing modern medicines from that point onward is a capital- and time-intensive

[1] http://www.phrma.org/pipeline
[2] Copley, Caroline. With biotech hot on Wall Street, VCs look to Europe for promising companies. *MedCity News*. August 7, 2013.

endeavor taking an average of 10 years and $1 billion to deliver a single new drug.[3] It is also a high-risk endeavor involving finding solutions to complex scientific and medical problems. However, when successful there can be no question of the reward. Over the last 20 years we have provided medicines that have vastly improved the quality and longevity of lives for patients dealing with diseases such as HIV/AIDS, cancer, and heart disease.

The U.S. Must Commit to Funding Discovery

A keystone to ensuring a robust life science industry is a national commitment to support basic research. Our nation's historical commitment to life sciences basic research is viewed as a precious jewel among nations. However, funding for the National Institutes of Health has been directly or effectively declining for the past several years with decreased or flat budgets that have not recognized inflation.[4] Basic research is the key to unlocking the mysteries of diseases and providing foundational discoveries that enable the biopharmaceutical industry to continue to research and ultimately develop new medicines for patients. Diminished support for basic research will lead to a smaller pipeline of next-generation medicines and impede our country's potential to transform how we treat diseases.

Research dollars provided by the National Institutes of Health to universities and colleges throughout the country also serve to train future scientists for 21st century jobs. Currently, the U.S. biomedical research sector supports over 5 million high-paying jobs in the United States and has tremendous potential for growth.[5] However, we must understand that our position as the global leader in medical science is constantly being challenged, and without a sustained commitment for scientific discovery, this is not a position that will be maintained.

Enabling Adoption of Modern Approaches to Drug Development & Approval Will Incentivize Investment

This Committee has heard and received written testimony regarding the enormous increase in requirements and duration of clinical trials.[6,7,8,9] These increases are especially acute for drugs designed to treat chronic diseases with larger patient populations. As a consequence, the cost of developing drugs has likewise been increasing. The Committee is right to ask whether these trends could be minimized by more effectively incorporating modern tools and approaches.

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[3] Adams CP and Bratner VV (2006) Spending on New Drug Development. *Health Economics.* 19, 13-141.
[4] Federation of American Societies for Experimental Biology. "Budget Cuts Reduce Biomedical Research." http://222.faseb.org/portals/2/PDFs/opa/5.16.13%20Funding%20Cuts%202-pager.pdf.
[5] Battelle Technology Partnership Practice. "Battelle/BIO State Bioscience Industry Development 2012". June 2012. http://ww.bio.org/sites/default/files/vebattelle-bio_2012_industry_development.pdf.
[6] Scannell JW, Blanckley A, Boldon H, and Warrington B (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews: Drug Discovery* 11, 191-200.
[7] Avik R (2012) The Stifling Cost of Lengthy Clinical Drug Trials. *Manhattan Institute.* http://www.manhattan-institute.org/pdf/fda_05.pdf.
[8] Tufts Center for the Study of Drug Development (12 April 2010) *PDUFA V Meeting.*
[9] Allison M (2012) Reinventing clinical trials. *Nature Biotechnology* 30 (1): 41-49

Venture funding is the life-blood of the small biotechnology companies working on disruptive science, and these venture-backed small biotechnology companies are the life-blood of innovative new medicines. In fact, a study published in 2010 found that in the United States a majority of scientifically innovative drugs were discovered or developed by biotechnology companies.[10] Large pharmaceutical companies may take over late-stage development and commercialization of many small biotech drug development programs. However, without innovative small biotech companies, many of today's innovative medicines would not exist, which in turn would not exist without the early-stage venture capital funding.

Venture capitalists invested $4.5 billion into private biotechnology companies in 2013, exactly equal to the prior 10-year average but down more than $1 billion from the pre-fiscal crisis 2007 peak. However, venture capital investment in early-stage life sciences companies has been under significant pressure over the last seven years. In fact, first-time financings in 2013 were down 35% from 2008 and in 2012 the number of early-stage financings dropped to a 15 year low.[11] A primary reason for this decline is the increased time and cost of developing new drugs and devices.

The decision to deploy capital is directly impacted by regulatory decisions and behaviors. Better enabling and encouraging FDA to utilize flexible approaches reflective of our understanding of the disease and patient being treated, as well as incorporation of modern approaches to development and approval, would have a positive impact on venture funding. For example, since the implementation of the Accelerated Approval pathway in 1992 over 80 drugs have been approved utilizing this pathway, including 29 to treat cancer and 32 to treat HIV.[12] This pathway allows for approval based on surrogate endpoints such as shrinking tumors or decreasing viral loads indicative of clinical benefits to patients with a commitment by the company to conduct confirmatory trials post-market to confirm the benefit. This has allowed oncology and HIV drugs to enter the public market in a significantly more effective manner. It is no coincidence that oncology has been and is projected to be one of the most active and innovative therapeutic markets.[13]

Likewise, in recent years FDA has shown an increased willingness to work with companies to develop more effective clinical development programs for rare diseases. This, along with added exclusivity for orphan drugs, has led to a significant increase in venture investment in rare diseases. The results are clear. In 2012, FDA reported that from 2007 to 2012 approximately one-third of the NMEs approved were drugs for rare diseases.[14] This trend continued in 2013, when 33% of NMEs approved were drugs to

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[10] Kneller, Robert. "The importance of new companies for drug discovery: origins of a decade of new drugs" *Nature Reviews Drug Discovery* 9, 867-882 (2010)
[11] PricewaterhouseCoopers, National Venture Capital Association. "MoneyTree Report." https://www.pwcmoneytree.com/MTPublic/ns/index.jsp

[12] FDA. FY 2012 Innovative Drug Approvals. December, 2012
[13] JP Morgan. 2014 Global Biotech Outlook. January 6, 2014.
[14] FDA FY 2013 Innovative Drug Approvals. December, 2012

treat rare diseases.[15] Again, we see that investment in early-stage, potentially breakthrough innovation in life sciences follows these signals, as venture investment in rare genetic diseases has significantly increased over the past few years.[16]

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) created a new Breakthrough Therapy designation that will provide increased interactions with FDA to ensure the most effective development and approval processes for promising new treatments. As of June 2, 2014 there have been 52 breakthrough designations granted by FDA.[17] Similar to statistics for Accelerated Approval, a majority of these designations have been given to oncology and rare disease treatments and therapies.[18]

The benefit of these programs has clearly been mostly realized in the oncology and rare disease space. As a society, while we celebrate these incredible successes, and indeed we *should* celebrate these successes, we have to ask ourselves what we want to do to improve how we treat the most egregious diseases affecting the greatest numbers our citizenry and long-term health costs, such as obesity, diabetes, and Alzheimer's, among others. As we examine the successes of these programs in terms of number of approvals for cancer and rare genetic diseases, we should endeavor to learn from the flexible and modern approaches utilized under these programs and work to apply them more broadly across therapeutic areas.

The fact is that while there are several examples where FDA has allowed for the utilization of novel endpoints, advanced tools such as biomarkers, and non-traditional clinical trial designs, the basis for such decisions is still poorly understood and inconsistent across review divisions. Without a more transparent and consistent approach as to what criteria such decisions are based on, the private sector will be hesitant to develop or utilize advanced approaches.

When it comes to chronic diseases with varying stages of progression and severity, there seems to be an actual reticence to employ modern tools and approaches. Recent ideas such as Special Medical Use and Europe's adaptive licensing pilot could serve to modernize our current system. Currently, our regulatory system is based on a philosophy that more information before approval is better. We must advance to a system that critically examines information required and determine whether it is actually informative as to the potential success of the drug in the real world. Creating approval pathways that enable the development of drugs for subpopulations of patients in areas like Alzheimer's and diabetes could be a game-changer. These approaches could serve to ensure the right drugs are getting to right patients in a much more effective manner.

From early-stage life sciences venture investment perspective, we know that when we start a company with breakthrough innovations in new areas of science and medicine it

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[15] FDA. Approved Drugs 2013

[16] Jarvis, Lisa M. Orphans Find a Home. C&EN Volume 91 Issue 19 | pp. 10-12. May 13, 2013.

[17] FDA

[18] Aggarwal, Saurabh (Rob). A Survey of Breakthrough Designations. *Nature Biotechnology* 32, 323–330 (2014)

will take a long time to turn that innovation into a drug that will reach patients and physicians and improve public health. The reality is the time required to put a drug on the market is, more often than not, longer than the length of our investment funds. Thus, when we create a new innovative company in a new area of science and medicine we are counting on the new medicine being developed being seen as important and valuable when it is still in the early stages of development. This is often referred to as the "proof of concept in the clinic," or Phase IIA. At that point, we are counting on the company and the product being sufficient to either take the company public on the NASDAQ or to have the company and/or product acquired by a pharmaceutical or larger biotech company.

The modern approach to regulation that exists now for cancer and rare genetic diseases allows this to work very well for three reasons. First, the regulatory process is more interactive, flexible, and reflective of the disease and patient being treated. Second, the amount, of time, and size of investment required to fund a company through 'proof of concept' is better understood. And, third, the next steps in our innovation ecosystem, larger companies and public investors, value the early-stage proof of concept data because they feel more confident about the development and approval process for these drugs. However, the same cannot be said for diseases such as obesity, diabetes, and Alzheimer's, where the time, amount of funds, and regulatory requirements are greater and there is less understanding about how to utilize modern tools and approaches. Without improving these processes, it is very difficult to imagine how early-stage investment can occur in such important areas.

In addition to the need for understanding the criteria which FDA will allow for utilization of modern tools, such as biomarkers and personalized medicine diagnostically defined subsets of a disease, there is also a need to provide incentives for the development of such tools. This is particularly important for the development of new diagnostics. It is imperative that regulatory processes for personalized medicine encourage early collaboration for the approval of therapeutics and companion diagnostics, as well as the development of advanced diagnostics in general.

Another, perhaps more critical, barrier to the advancement of diagnostic development is the fact that there are no consistent reimbursement policies for diagnostics. Congress recently passed the Protecting Access to Medicare Act of 2014 which included the Improving Medicare Policies for Clinical Diagnostic Laboratory Tests provision. This provision is an important and positive step forward. How transformative depends on whether the potential benefits are realized and implemented in the regulations. There remains substantial uncertainty in the private and public world of reimbursement for molecular diagnostics. This uncertainty continues to hold back investment in breakthrough personalized medicine innovation that could significantly advance how we develop drugs and treat patients with critically important diseases such as Alzheimer's, diabetes, and others.

I would like to recommend that the Committee consider a process whereby the Centers for Medicare and Medicaid create a program for diseases important to the public health

with high unmet diagnostic needs. This would be particularly useful in advancing how we develop treatments for Alzheimer's and diabetes. Diagnostics has the potential to play a much more significant role in helping to identify subsets of patients suffering from either advanced stages of disease progression or with different benefit/risk profiles based on genetics. By identifying these subsets of patients we will be able to develop treatments for these diseases and patients in a much more effective manner. However, in order to fully realize these benefits we must provide clear reimbursement policies for these diagnostics that reflect the value the diagnostic provides to patients, providers, and our nation's health care system overall. One approach would be to look at disease areas critical to our nation's health care system such as Alzheimer's or diabetes. Establishing a payment policy for diagnostics in these disease areas for some meaningful determined period of time would serve to incentivize development of such products. Clear payment polices of personalized medicine tools combined with modern regulatory approaches would advance personalized medicine by leaps and bounds.

Utilization of Real-World Data: A Life-Cycle Approach to Drug Development

We currently have a system that requires a life-cycle approach to drug development with increasing abilities to monitor the safety and efficacy of drugs in the real world. However, we have not turned any of these new abilities to collect and share information into tools to advance drug development and improve how we treat patients. As we think about how we can accelerate drug development in chronic diseases such as diabetes, obesity, and Alzheimer's, and as we consider what is the evidence required for approval in such areas, we should keep in mind that real world data post-approval may be a very effective tool in understanding the scope of such drugs and may allow us to get to approval of these important new medicines more quickly. We should be actively working to integrate real-world data into the drug development and review process, and to achieve the right balance of what data we are requiring before and after approval. These approaches would help ensure patients have access to new medicines more expeditiously and could serve to support expanded indications in a more effective manner.

To ensure the promise of such real world data is realized, we must incorporate it as scientifically appropriate in the drug development process and make sure such data is available for use. As such, we must advance our healthcare system to one that has inter-operability capabilities that would enable more efficient use of electronic medical records with the real-world data required. We must also ensure that our systems have the ability to exchange such information in a privacy-protected manner. A balkanized set of such data would be missing an opportunity to support tremendous innovation in our health care ecosystem.

Conclusion

These are just a few incentives that could serve to advance how we develop medicines and treat patients. There are other critical policy areas that have the ability to impact or weaken the life science ecosystem not mentioned in this statement, but I would be happy to discuss these areas further with this Committee. For example, we must ensure that intellectual property is protected. There is no investment if the primary asset of an industry is not protected in a manner that allows for returns on investments. Data

exclusivity of sufficient lengths of time can also be a powerful incentive, and we could consider aligning small molecule data exclusivity to the 12 years for biologic drugs, as the current 5 years of exclusivity for small molecules does not provide incentive from a venture capital perspective. We must work to ensure we encourage investment in small, innovative pre-revenue life science companies.[19] Lastly, we must ensure that reimbursement policies are determined in the context of the disease and patient being treated and the impact of a drug is evaluated over appropriate time lines. We must not create a system that will severely diminish investment in the next generation of cures and treatments. Thank you for the opportunity to share my thoughts and I would be happy to answer any questions.

[19] CSBI. http://www.smallbusinessinnovators.org/

Mr. PITTS. The chair thanks the gentleman and now recognizes Mr. Carusi 5 minutes for an opening statement.

STATEMENT OF MIKE CARUSI

Mr. CARUSI. Chairman Pitts, Representative Pallone, members of the subcommittee, thank you for the opportunity to testify today on behalf of the National Venture Capital Association. Chairman Upton, Representative DeGette, thank you for spearheading the 21st Century Cures Initiative. It is important work.

My name is Mike Carusi. I have been in the venture capital business for over 16 years. Over the course of my career, I have had the privilege of helping innovative companies develop therapies for some of the most daunting diseases of our time including heart disease, diabetes and cancer.

I am here today to share my perspective on what is happening with medical technology innovation. Simply put, we are facing a crisis, and the continued leadership of this committee is needed more than ever. Without changes in public policy, the United States will no longer lead the world in developing lifesaving treatments, and American patients face a grave risk of losing access to these innovative cures.

The promise and importance of innovation has never been greater. Our understanding of the origins of disease and human physiology are growing. We see dramatic advancements in engineering, material science, information technology. As the population ages, new and improved medical technologies can play a critical role in not only helping to improve patient care but also in reducing long-term costs as well. But despite our patients' needs and our ability to meet them, funding for innovative medical technologies has declined substantially in recent years. As Congresswoman Blackburn noted, between 2007 and 2013, medical device venture investments fell by a total of 40 percent. In 2013, we witnessed the lowest level of medical device initial funding activity in more than two decades with just 44 companies receiving first-time funding—44 companies.

Poor investment returns have resulted in institutional investors such as universities, pension funds and foundations fleeing the device sector. It is important to note that these are the very groups that we get our money from. As a result, an estimated 70 percent of all medical device venture investors have or will exit the business over the next 5 years, and most of these departures are not by choice.

Another equally troubling fact is that for those with capital, we are shifting more and more of our resources overseas. In my firm's case in particular, 25 percent of our future investment will focus out of the United States. This is a big change from the way we have done business in the past.

So why is this shift occurring? First, access to capital. Countries like Ireland and Singapore are offering powerful economic incentives to groups like Lightstone to invest. Second, and more importantly, the regulatory path in these markets is simply faster and more predictable. It is now commonplace for our companies to seek regulatory approval and commercialize new products in other markets ahead of the United States.

We have talked at length about the path to FDA approval, about the challenges in this path, about the delays in the unpredictability, and I am happy to say that progress has been made to begin reducing these regulatory barriers. The 2012 FDASIA bill included a number of important provisions which are beginning to have a positive effect. The veterinarian community and medical device incubators also has enjoyed a productive dialog with CDRH Director Shuren and other members of his leadership team in working to further improve the medical device regulatory process. We are by no means done and we have more work to do to continue to build on this progress, but FDA has no longer become the greatest obstacle to innovation. That obstacle is now reimbursement.

Obtaining coverage and reimbursement for innovative products has become an increasingly difficult process that can add another 3 to 5 years to the development of a new product. It is a process that lacks transparency, predictability and consistency. I have experienced this firsthand—changing standards for data, no clear benchmarks, an ever-moving bar. It is an extraordinarily frustrating process that you simply need to go through once to clearly see that the system is broken.

In my written testimony, I have included several specific recommendations on how we can improve on the system. At its core, I would bring us back to transparency, predictability and consistently, similar themes that we echoed in our discussion on FDA. These are the three hallmarks that we need as investors to have confidence in moving ahead.

Again, it is important to underscore that none of these steps alone will ensure a reinvigorated medical technology ecosystem. There is no silver bullet. But I believe a renewed focus on drastically improving the coverage and reimbursement situation is sorely needed.

Again, thank you for the opportunity to testify today. I love what I do, I love the process of innovation, I love developing treatments for patients. That is why the work of this committee is so important and so necessary. We look forward to working with you, and I am happy to answer any questions you might have.

[The prepared statement of Mr. Carusi follows:]

Testimony of Mike Carusi
Advanced Technology Ventures

House Committee on Energy and Commerce
Subcommittee on Health
Hearing On:
"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients"
Wednesday, June 11, 2014

Introduction

Chairman Pitts, Ranking Member Pallone, my name is Mike Carusi. I am a General Partner of Advanced Technology Ventures (ATV), based in Palo Alto, California, where I focus on investments in the biopharmaceutical and medical device sectors. I also serve as a General Partner and Team Leader for Lightstone Ventures (LSV), a recently established venture capital fund focused exclusively on healthcare investments and opportunities.

I also am a member of the National Venture Capital Association (NVCA). NVCA is the voice of the United States venture capital community, representing nearly 400 members and advocating for public policies that encourage innovation and drive entrepreneurial investment. I want to note that my testimony reflects input from the NVCA, the Medical Device Manufacturers Association (MDMA) and Advanced Medical Technology Association (AdvaMed) and generally is consistent with the views of those organizations.

I am an engineer by training who made the transition to Venture Capital in 1998. My professional career has been devoted to investing in early stage medical device and biotechnology companies. During my time in venture, ATV and LSV have funded a total of 40 companies with my having personally led 20 of these investments. As a Venture Capitalist, I provide not only capital but also guidance. My passion is helping these innovative companies develop therapies for some of the most daunting diseases and medical conditions of our time.

I have been very fortunate to be a part of numerous companies that have been at the leading edge of innovation. These include: GI Dynamics a medical device company that has developed a novel device-based approach in the treatment of Type II diabetes; Ardian, a medical device company that has pioneered the field of renal denervation in the treatment of refractory hypertension; and Plexxikon, a biopharmaceutical company that has developed a drug that has revolutionized the treatment of melanoma.

It is extremely challenging, but also extremely rewarding work. Not only do I have an opportunity to help build companies, I also have the ability to help cure disease and have an impact on people's lives. I am reminded of this every time I receive a note from a mother, a daughter, or a husband who has had a loved one who has been successfully treated by one of my companies' products.

The members of this Committee have a long history of working together to find practical bipartisan solutions to some of our nation's most pressing challenges. For example, in 2012, the Committee enacted the Food and Drug Administration Safety and Innovation Act (FDASIA), which not only reauthorized the medical device and prescription drug user fee programs but included a number of important provisions to speed the approval process at the Food and Drug Administration (FDA) so that patients would have more rapid access to life-saving treatments. I specifically want to thank you, Chairman Pitts and Ranking Member Pallone, for your continued leadership. I also want to commend Chairman Upton and Representative DeGette for recognizing that additional measures are needed to spur innovation and better coordinate activities across key government agencies to unleash the full promise of medical technology to truly benefit America's patients.

Your leadership is needed more today than ever. The medical technology industry is facing a crisis. Without changes in public policy, the U.S. will no longer lead the world in developing life-saving treatments, and American patients face a grave risk of losing opportunities for cures.

Background on the Venture Capital Community and Support for Medical Innovation

The United States has been the global leader in medical technology innovation. Our medical device innovators have pioneered novel therapies such as drug eluting stents to treat cardiovascular disease, insulin pumps to treat diabetes, endovascular coils to reduce the incidence of hemorrhagic stroke, and percutaneous heart valves to treat aortic valve disease. As noted previously, my firm and I have been very fortunate to be a part of several of these breakthroughs. These therapies clearly have improved the lives of patients. They also have benefitted a wide range of additional stakeholders within the healthcare ecosystem including physicians, payors, hospitals, foundations, and universities.

For the past 50 years, the development of innovative medical devices has been driven by small, entrepreneurial companies often fueled by venture capital. In fact, 80 percent of medical device companies have fewer than 50 employees, and 98 percent have fewer than 500.[1] Venture capitalists raise capital from institutional investors, such as pension funds, endowments, and foundations, and invest these funds in promising, young start-up companies. When we do our job well, we help create companies with high-quality jobs that provide patients and physicians access to innovative medical technologies. We also generate financial returns for our investors.

[1] "Medical Technology and Venture Capital: A Fruitful Yet Fragile Ecosystem," MDMA and NVCA, June 2009, http://www.medicaldevices.org/node/656.

This allows universities to educate more students, foundations to care for their constituents, and pension funds to meet the needs of their retirees. In short, the U.S. medical technology ecosystem is an incredible win-win system.

Industry Challenges

We live at a time when the promise and importance of innovation has never been greater. Our understanding of the origins of disease and human physiology are growing significantly. We are witnessing dramatic advancements in our engineering capabilities, breakthroughs in materials science, and exponential growth in the use of information technology. As the population ages and the pressure to improve the value equation of health care mounts, new and better technologies can play a critical role in helping to reduce long-term costs and improve patient care. Simply put, medical technology advances have the potential to be a central part of the solution to the many challenges facing the U.S. healthcare system over the years to come.

Ironically, despite these growing needs and our scientific ability to meet them through continued innovation, the funding of medical technologies has declined substantially in recent years. Between 2007 and 2013, medical device investments fell by a total of 40 percent[1]. While other sectors, such as information technology, witnessed a recovery after the financial crisis, medical device investing has continued to suffer. Of even greater concern, the decline in investment for companies at the initial phase of financing has been even more dramatic. In 2007, the Money Tree report by PricewaterhouseCoopers and the National Venture Capital Association (based on data from Thompson Reuters) showed 98 companies amassing approximately $576 million in initial venture capital. Since then, there has been a 50 percent reduction in the number of device companies receiving initial venture capital investment and an approximate 70 percent drop in the amount of capital invested. In 2013, we witnessed the lowest level of medical device initial funding activity in more than two decades. Last year, only 44 new venture device companies raised a total of $163 million compared to 2007's 98 companies, according to Money Tree.[2]

As noted earlier in my testimony, I have a very strong personal commitment to improving the lives of patients—and a long track record to back that up. This is true of many of my venture colleagues as well. However, we also have a fiduciary duty to the universities, pension funds, foundations and other institutional investors whose money we manage and invest. Over the past 10 years, the average returns for medical device investments have simply fallen short of expectations. These poor returns have resulted in institutional investors fleeing the sector. An estimated 70 percent of all medical device venture firms have or will exit the business over the next five years. Let me repeat this, 70 percent of all device investors are going away. This is an enormous problem. As venture funding falls, innovation falls.

[2] NVCA/PWC MoneyTree Survey, "VC Investments Q4 – MoneyTree – National Data", http://nvca.org/index.php?option=com_content&view=article&id=344&Itemid=103

Our recent fund-raising experience for Lightstone Ventures serves as a powerful reminder of the challenges our sector currently faces. Despite having outstanding returns, our fund-raising effort was extraordinarily difficult. We ultimately were successful, but it took two years and four hundred thousand miles of travel to get it done. Of note, approximately 25 percent of LSV's future investment activities will focus outside of the U.S. This is an important change from how we operated previously.

There are several reasons for this change. First, countries such as Ireland and Singapore, are offering powerful economic incentives to groups like LSV to invest outside of the U.S. Second, and more importantly, it has now become commonplace for our companies routinely to seek regulatory approval and commercialize new products in other markets ahead of the U.S. The regulatory path in these markets is simply faster and more predictable. As our companies migrate outside of the U.S., so must we. LSV, for example, just announced the opening of a Dublin office as well as a major strategic initiative in conjunction with the Irish Government. Clearly, we as venture capitalists would prefer to stay closer to home, but the U.S. path to market has become too costly and too unpredictable. This trend can be reversed, but change is needed.

Regulatory Challenges

To be clear, there is no single cause for the challenges that face medical device innovation. I believe the industry is partly responsible for its recent performance. Too many companies developed too many products that were too incremental in nature. These products were not disruptive enough to merit adoption. However, it is important to ask why the industry chose to go down this path. As the time and cost to bring a product to market increases, investor returns decrease. Investors were attempting to tweak a broken model.

In a recent survey conducted by NVCA, 42 percent of health care investors expressed that they decreased their investment in medical device companies due to the longer time frames to regulatory approval.[3] Since 2005 the timeline to an approval decision has become substantially lengthier, resulting in millions of dollars of extra capital spent. A small, venture-backed company typically spends $500,000 to $2 million per month in operating costs as it conducts clinical trials and awaits regulatory approval. A six to twelve month delay can significantly increase the amount of money necessary to see the product through to market approval.

As we have discussed with this committee and the broader policymaking community at great length, the path to regulatory approval in the U.S. has become increasingly difficult to predict. Unexpected regulatory delays increase both the time and capital required to bring products to market. These increases, in turn, are forcing many venture capital firms, and those institutions that support them, to move away from medical device investing. Although LSV remains committed to the sector, we have had to readjust our investment strategies and tactics. I

[3] "FDA Impact on US Medical Technology Innovation", Dr. Josh Makower, November 2010, http://nvcaccess.nvca.org/index.php/topics/public-policy/155-fda-impact-on-innovation-study-out-today.html.

personally have not invested in a new medical device company in over two years. Subsequently, we now are looking more aggressively outside of the U.S. We also are seeking ways to help limit risk. This includes running early knockout experiments, sticking to known clinical pathways, and only backing the most experienced of teams. It also means limiting our investments to those therapeutic areas where the FDA has proven to be more rational and collaborative. Given these tight filters, we likely will fund only one deal out of a hundred. These are very long odds for aspiring innovators. Perhaps most disheartening, many of the ideas that are not funded are not because of a lack of clinical importance or necessity, but because the anticipated regulatory challenges deter financing. Good ideas are being passed over, which is never a recipe for success.

Fortunately, we have made progress in recent years. NVCA applauds Congress, and the members of this Committee, for working in a bipartisan effort to make significant improvements to the FDA process. The new medical device user fee goals included as part of the 2012 FDASIA bill should help to improve this situation. FDASIA's provisions regarding breakthrough technologies also should go a long way toward reducing timelines, without compromising patient safety. Other important improvements that were included in the bipartisan FDASIA legislation include clarifications to the standards that the FDA should use in making future regulatory decisions around the risks and benefits of new products, as well as greater flexibility in the use of outside experts to help speed reviews.

Additionally, I would like to thank Commissioner Hamburg and Center for Devices and Radiological Health (CDRH) Director Shuren for listening to concerns from the venture capital community and working in a collaborative manner to help improve the regulatory process for medical devices within the U.S. The efforts to implement an "innovation pathway" and the recent guidance document outlining patient benefit vs. risk as the clear basis for PMA and de novo device approvals are specific examples of improvements that Dr. Shuren and his staff have undertaken. NVCA also applauds CDRH's 2014 Strategic Goal to provide patients in the U.S. with first in the world access to new medical technologies. These are important advancements that I truly believe will help to maintain this country's lead in medical device innovation.

With that said, we have more work to do. We need to make sure that steps are taken at the regulatory level to ensure that the goals of these new legislative provisions are fully realized. Specifically, there needs to be continued focus on management improvement and reviewer training to ensure consistency and timeliness of reviews. We need to explore opportunities for streamlining the Independent Review Board (IRB) approval process, improving the Investigational Device Exemptions (IDE) process, reducing unnecessary preclinical trial data, and improve the process for undertaking first-in-human studies here in the U.S. Lastly, there should be sustained focus on improving procedures for the evaluation and approval of combination devices. These are important additional steps that all need to be taken.

Reimbursement Challenges

Although we have made important progress in working with Congress and the FDA to help ensure a more predictable regulatory process, this is only one of the many challenges we face. In order for the promise of medical technology innovation to be fully realized, we must build on the spirit of collaboration we have developed in resolving regulatory obstacles and address what has become an even greater challenge facing medical device innovation: reimbursement.

After our companies have worked through the costly and timely process of receiving FDA approval, they then must set their sights on securing coverage and reimbursement. This is an equally complex and unpredictable process which can add another three to five years to the development of a product. This means three to five more years before patients can actually benefit from a new product and before the company can generate a meaningful revenue stream. Each phase of the reimbursement process (coding, payment and coverage) has its own unique set of challenges. As with the FDA in years past, the biggest challenge we face is the lack of transparency, predictability, and consistency of the process. Moreover, the data requirements payors impose before granting coverage are often so high and unclear that they discourage investment in and development of promising treatments. This is true of both government programs, as well as private payors—which often follow the decisions made by the Medicare program.

The overall process of obtaining coverage and reimbursement represents a classic "chicken and the egg" dilemma for the investment community. On the one hand, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it. On the other, physicians and hospitals will not agree to use the product unless they get paid. Equally challenging, the data and utilization requirements are ambiguous at best.

There is increasing evidence that payors are raising the standard for coverage determinations. One study by Tufts University researchers found that the probability a therapy considered for national coverage under the Medicare program will be approved dropped by more than 60 percent between 1999 and 2007. When coverage was granted, the scope was more limited than the indications approved by the FDA in 40 percent of the cases studied.[4] While Medicare national coverage determinations represent a relatively limited universe, we are finding that both private payors and government programs are increasing the bar for coverage and reimbursement decisions. What is most troubling is that it is often not clear where that bar lies.

I have had two experiences, recently, where a company in which ATV invested faced this very challenge. In one instance, we were told to come back time and time and again with more data. Each time we met the deliverable. Each time we were asked for more. There was seemingly no

[4] Chambers J.D., Morris S, Neumann P, and Buxton M. (March 2012) Factors Predicting Medicare National Coverage: An Empirical Analysis. *Medical Care Journal*, 50(3).

end to the process. In another instance, we were told that utilization of our device in 5,000 patients was not enough. We came back again with 10,000 patients. Not enough. We came back again with 15,000 patients. Not enough. Once again, the process appeared to be unending. My venture colleagues and I increasingly are facing this type of situation. This is clearly an area of medical innovation where our public policy leaders can help lead the way towards a more open and transparent process.

In short, we need to make the coverage process in both the public and private payor context more open and transparent. We need to take steps to expedite coverage and reimbursement decisions. We need to foster improved collaboration among the innovator, payor and patient communities. And we need to ensure that our government programs are more receptive to rapid coding and coverage of new technologies. Below, we include several areas where we believe progress could be made and which would help to improve the process of medical device innovation in the U.S.

Policy Recommendations To Improve the Coverage and Reimbursement Climate

As I indicated previously, just as there is no silver bullet to revitalizing U.S. investment in innovative medical devices, there is no simple solution to improving the reimbursement climate in the United States. NVCA recognizes that we must balance our nation's need to better address the growth in overall health care costs while at the same time ensuring that patients have access to life saving technologies. These two goals, however, do not need to be mutually exclusive.

We believe that several important steps can, and should, be taken to improve the coverage and reimbursement climate for medical technologies. As mentioned earlier, progress can be made if we begin by encouraging our public payor programs to take a page from the collaborative and more transparent environment we have begun to create in the regulatory approval process. First, in building on the work of this Committee with the FDA, we believe that the Medicare program should be required to take into account patient perspectives on risk and benefit in making coverage and reimbursement decisions. In addition, we believe that Medicare should be encouraged to expand opportunities for participation by patients, providers, innovators and investors in meaningful dialogue about coverage determinations beyond the existing MedCAC advisory role in which some patient representatives are now allowed to participate.

Second, Congress should consider expanding the Medicare program's overall mission to encourage the program to help promote and adopt improved treatments for beneficiaries. This would be similar to the FDA mission statement providing that the agency should advance public health by "helping to speed innovations that make medicines more effective, safer, and more affordable." Broadening the focus of the Centers for Medicare and Medicaid Services may help to achieve a more appropriate balance that could truly benefit the patients Medicare serves.

There are some additional concrete steps we urge the Committee to consider. These include streamlining the requirements of the Coverage with Evidence Development (CED) program to better align with FDA post-market data collection and study standards. The administration of the CED program should also be re-oriented toward expanding and speeding coverage of promising treatments, rather than posing an additional barrier. Too often, in practice, CED requirements simply add to the burden of data collection and, as a result, delay patient access to new therapies.

In addition, we believe Medicare's process for assigning billing codes to new technologies can be streamlined. As you know, obtaining codes is often a prerequisite to coverage and reimbursement and, often, the process of obtaining codes can take up to18 months or more following FDA approval. This is simply too long for patients to wait for new cures and imposes yet another unnecessary roadblock to investment in medical technologies.

Finally, we too believe that there are opportunities to improve overall value in the Medicare program by utilizing new provider risk-sharing arrangements and value-based payment models. We know that the Centers for Medicare and Medicaid Innovation (CMMI) is experimenting with a range of alternative payment models (APM) and that there is considerable interest among policymakers in evolving the Medicare program from a fee-for-service system that compensates providers based largely on volume to one that reimburses for value. At the same time, new forms of APMs and provider risk-sharing arrangements can create strong, often overpowering, incentives for cost reduction at the expense of patient access to treatments and cures. In part, this is because there are significant gaps in the current measures used to reward system quality. Therefore, we urge greater oversight over these innovative payment models in Medicare. We also believe it is important to provide greater transparency around measures upon which payments will be based and to ensure that payment models are flexible enough to accommodate new, improved and innovative treatments, even when those treatments may come at a higher cost than outdated therapies. Again, none of these steps alone will ensure that our nation's medical technology innovation engine is again working at full speed. But, a renewed focus on drastically improving the coverage and reimbursement situation at least in our nation's major public programs can help repair the medical device research and development ecosystem.

Medical Device Tax Repeal

On a related note, while I know that this Committee has been focused on regulatory and reimbursement challenges facing the medical community, I also want to mention just briefly the importance of repealing the medical device tax, which has overwhelming bipartisan support in the House of Representatives. This flawed policy adds yet another burden to medical device innovators and is a major deterrent to developing the cures and technologies of tomorrow.

Conclusion

Again, thank you for the opportunity to testify today. We greatly appreciate the work that the Energy and Commerce Committee has done to improve the innovation ecosystem and we welcome the 21st Century Cures initiative. With that said, more work is needed. We need to continue to build upon the progress we have made with improvements at the FDA and the regulatory approval process. Equally important, we need to greatly improve the reimbursement climate within this country. Lastly, we need to repeal the medical device tax. With these improvements, we can continue to ensure that the U.S. remains a global leader in the development of life saving medical device therapies. Without them, I fear medical device innovation will continue to leave our shores. The choice is ours.

Mr. PITTS. The chair thanks the gentleman and now recognizes Dr. Miller 5 minutes for an opening statement.

STATEMENT OF STEVEN MILLER

Dr. MILLER. Thank you, Chairman Pitts, Ranking Member Pallone and members of the committee.

Mr. PITTS. Can you push the mic?

Dr. MILLER. I appreciate the opportunity to testify today. I am the Chief Medical Officer for Express Scripts but a former transplant nephrologist and former Vice President and Chief Medical Officer for Washington University and Barnes Jewish Hospital. I started my career in primary drug discovery and hold many patents and have been with Express Scripts for the last 9 years. Express Scripts is the largest pharmacy benefits manager, administering the benefits for 85 million Americans on behalf of clients including health plans, large and small businesses, and the Department of Defense. Each day we work to make the use of prescription drugs safer and more affordable.

The current system works very well to drive innovation. There is more than 5,000 drugs in human testing in the United States today, more than any time in my 30-year career. But for payers, this is concerning. Whether highly or mildly innovative, these advances come at enormous cost to patients and payers. These new therapies cost tens of thousands of dollars per patient, and the challenge is made clear by one recent approval, Solvadi. Solvadi is a new treatment for hepatitis C. In the first quarter of 2014, its sales exceeded $2 billion. Cost of Solvadi varies by nation, but in the United States, it is $84,000, or $1,000 per pill. You compare that to Canada or Europe where it is $55,000, and in Egypt, $900, which is less than a single dose in the United States.

Solvadi is a breakthrough with a high cure rate but varied analysis suggests that Solvadi may not be worth the price. A study from the California Technology Assessment Forum found that even over a 20-year horizon, the cost-benefit is only two-thirds of the original $84,000.

Solvadi is valuable to patients worldwide but should it be the United States' role to pay the lion's share where Solvadi manufacturers have the most incentives available to promote innovation. Americans will pay more for the medicine than anywhere else. Incentives available for Solvadi or other include, one, market exclusivity. In addition to the usual patent protection afforded to high-tech products, brand drug manufacturers receive a period of exclusivity under Hatch-Waxman where they are protected for competition. Two is they get breakthrough approval designations. Since 2012, drug makers have had the ability to see a breakthrough therapy designation by the FDA to expedite the review of new drug applications that demonstrate substantial improvements over existing therapies. Three, we have a free market to sell medicines. Unlike other nations, the new drug approval process doesn't include cost-effectiveness comparisons. Manufacturers are free to sell their medications at prices they determine without government intervention, validation or approval. And four, NIH support. The NIH supports drug makers with bench science, basic research and support for clinical trials.

The price of Solvadi should be disappointing to lawmakers, who have worked to foster innovation and encourage a marketplace in the United States for brand drugs. Any action that Congress considers should explore the need for an environment where America doesn't pay the lion's share for research and development that is benefited worldwide. Congress should consider the proven ideas. One: Support NIH with additional funding. Drug discovery begins with excellent work by the team at the NIH. Two: Support the FDA. Given the success of Fast Track, accelerated approval, priority review programs, without compromising safety and effectiveness of drugs, these hastened timelines can become the norm of new drug approval if additional funding is provided. And three: Reserve marketplace incentives for true innovations. Market exclusivity is invaluable to drug makers and it should only be granted to new drug applications that substantially improve upon existing therapies. What better way to promote innovation than to more carefully grant monopolies to drug manufacturers?

In conclusion, existing incentives for innovation are working. Today we have more companies doing drug discovery than ever. The industry is healthy and profitable. Express Scripts is concerned by the idea that rewarding certain types of drug development with additional market exclusivity will pervert the commercial market for prescription drugs. It will inhibit innovation. It artificially restrictions competition and it affords the same reward to breakthrough therapy as to less innovative product improvements. Most importantly, it places the burden for funding this additional incentive solely on the back of payers of health care rather than socialized equally by society through the tax code. Proposals that seek to expand market exclusivity in any situation need to be approached very carefully, very narrowly to ensure the right solution to the underlying problem.

Thank you very much for this opportunity.

[The prepared statement of Dr. Miller follows:]

Testimony of Steven B. Miller, MD, Senior Vice President and Chief Medical Officer, Express Scripts

House Energy & Commerce Committee
Hearing on "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients"

June 11, 2014

Chairman Pitts, Ranking Member Pallone, and Members of the Committee, I appreciate the opportunity to testify today. I am the Chief Medical Officer for Express Scripts. Express Scripts is the nation's largest pharmacy benefit manager, administering the benefits for more than 85 million Americans. Each day, we work to make the use of prescription drugs safer and more affordable. With the country facing hundreds of billions of dollars of prescription-related waste each year from costly drug, pharmacy and health choices, our mission remains as relevant as ever.

Today, we manage prescription benefits for tens of millions of Americans on behalf of thousands of clients, including health plans, large employers, small businesses and other plan sponsors. Employers, unions and government organizations throughout the nation rely on our services. We are committed to our members achieving better clinical outcomes and dedicated to delivering better financial outcomes for plan sponsors.

Innovative therapies are critical component of the prescription drug benefit. As these break-through therapies come to market, our clients, public and private, expect us to deliver innovative benefits to meet their needs and ensure appropriate use of these therapies. Critical to freeing up dollars in the prescription drug benefit to pay for these new cures is the ability to harness the use of generics—and in the future, biosimilars—where and when we can. Generics truly have been the success story of the past 30 years: driving innovation through competition.

To that end, Express Scripts supports a strong, fully-funded FDA, which is equipped to efficiently evaluate and approve new brand and generic medicines while appropriately ensuring patient safety. The Agency must have the resources to assure timely and predictable access to both brand and generic medications. We applaud the FDA for increasing the pace of drug approvals and providing increased information to payers and consumers about drug evaluations. We also support federal investment in biomedical research at the National Institutes of Health to ensure the US remains at the forefront of innovation and discovery. This is particularly important for basic scientific research.

The current system works very well to drive innovation, with more than 5,000 drugs in human trials for 74 distinctly different diseases[1]. Adding to the complexity for patients and payers is the manufacturer community and FDA focus on specialty medications. In 2013, 19 of the 28 approved new therapeutic drugs were specialty medications – nearly 70% of new drug approvals. For the last three years, specialty drugs have been the majority of FDA new drug approvals.

Some of these new specialty drugs approved in 2013 are remarkable:

- Eight new cancer drugs were approved, including oral formulations and gene-specific targeted therapies (e.g. Tafinlar® and Mekinist®).
- For the first time, medications were approved under the FDA's new Breakthrough Therapy expedited approval program (e.g. Gazyva™, Imbruvica™, Solvadi™)
- At the same time, 2013 FDA drug approval data shows some instances that fall short of true innovation:
- In anticipation of the loss of patent protection for an inhaled solution that treats respiratory conditions, the manufacturer launched a new formulation of the same product with a new administration mechanism.
- The FDA approved zero biosimilars.

Whether highly or mildly innovative, these advances come at an enormous cost to patients and payers. These new therapies cost tens of thousands of dollars per patient. The challenge to payers is made clear with one recent new drug approval: Solvadi™.

Sovaldi is a new oral treatment for hepatitis C, a debilitating blood-borne disease of the liver affecting some 3 million Americans. The launch of Sovaldi has been the most successful in the history of the pharmaceutical industry. In just the first quarter of 2014 alone, the drug generated sales in excess of $2 billion. It's projected to become the largest selling drug in the world by the end of this year. And while the cost of Sovaldi varies by nation, the cost for a course of treatment in the United States is $84,000, or $1,000 per pill. The cost is approximately $55,000 in the U.K. and Germany. In Egypt it is $900 for a full course of treatment, still less than the cost of one Sovaldi pill in the U.S.

Not every patient diagnosed with hepatitis C needs to take Sovaldi. Hepatitis C is typically a very slowly progressing disease. Some infected patients do not manifest serious symptoms for decades after infection. Many hepatitis C patients are "warehoused," a common practice among hepatologists who take a "watchful waiting" approach with caring for hepatitis C patients until there is a clear need for treatment.

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[1] Pharmaceutical Research and Manufacturer Association. "Explore the Latest Progress on Medicines in Development." (2014)

Clinically speaking, Sovaldi is a breakthrough in reducing the amount of hepatitis C virus to undetectable levels, with a "cure" rate of over 90 percent. However, various analyses suggest that Sovaldi may not be worth the price. In fact a new study from the California Technology Assessment Group found that even over a 20-year time horizon, the cost-benefit is only about two-thirds of the original $84,000 cost.

The high cost of Sovaldi has created a tipping point in the dialogue about fairness in drug pricing. Payers are galvanized around this issue like none before. Many payers did not budget for such a high cost drug and are now having to make tradeoffs between covering the drug and covering other basic treatments for their plan members. State budgets, in particular, are taking on the brunt of the cost at a time when state budgets have already been significantly stretched, as a third of the patient population is uninsured, underinsured and/or are currently incarcerated.

To be clear, improved sustained viral response from Solvadi™ is valuable to patients worldwide. But should it be the US' role to pay the lion's share of this innovation? To be clear, innovations like this should be rewarded handsomely, but within the bounds of what the country and taxpayers can afford, and we believe the current price for Solvadi violates these boundaries. In the United States, where Solvadi's manufacturer has the most incentives available to promote innovation, Americans will pay more for the medicine than anywhere else in the world. Some of these incentives include:

Market exclusivity. In addition to the usual patent protections afforded to high tech products, brand drug manufacturers receive a period of exclusivity under the Hatch-Waxman Act (or BPCIA for biologic therapies), where they are protected from competition on their product. These exclusivities aren't challengeable in court. And they are uniquely American.

Breakthrough approval designations. Congress acted to encourage speedy approval of "breakthrough" medicines when it passed the Food and Drug Administration Safety and innovation Act in July, 2012. Since that time, drug makers have had the ability to seek a *breakthrough therapy* designation by the FDA to expedite the review of new drug applications that demonstrate substantial improvement over existing therapies. This expedited approval is above and beyond the *Fast Track* approval program and is in addition to Accelerated Approval and Priority Review programs at FDA.

Our free market to sell medicines. Unlike other nations, the new drug approval process doesn't include a cost-effectiveness comparison. Manufacturers are free to sell their medications at prices they determine without government intervention, validation or approval.

NIH support. The NIH supports drug makers with bench science, basic research, and supporting clinical trials.

The price of Solvadi should be insulting to lawmakers who have worked to foster innovation and encourage a marketplace in the United States for brand drug makers. The challenge before Congress today is whether more needs to be done to promote innovation. Any action that Congress considers should explore the need for an environment where America doesn't pay the lion's share of research and development worldwide.

Some additional ideas that the Committee and Congress should consider include:

Support NIH with additional funding. Drug discovery begins with the excellent work by the team at NIH. Their exploration of scientific cures is the backbone of new drug discovery. Congress should consider ways to support NIH with additional funding that will serve: drug makers, patients, and the payers who afford the cures.

Support the FDA. The FDA does an incredible job and needs to be as scientifically advanced as the most developed company they regulate. Additional FDA funding is essential to expanding review programs and speeding new drug approvals. Given the success of *Fast Track*, *Accelerated Approval*, and *Priority Review* programs, without compromising the safety and effectiveness of drugs, these hastened timelines could become the norm for new drug approval if additional funding is provided.

Reserve marketplace incentives for true innovation. Market exclusivity is invaluable to drug makers and it should only be granted to new drug applications that are substantially and significantly improved upon existing therapies. The goal should be for companies to direct funding to the innovative discovery of new cures rather than rewarding "me too" products. What better way to promote innovation than to more carefully grant monopolies to drug manufacturers? When these marketplace protections aren't guaranteed, manufacturers will strive to ensure their products are truly superior.

The balance between access to lower cost generic medicines and incentives to innovate new and better medicines as embodied by the 1984 Hatch-Waxman Act is working. Today we have more pharmaceutical and biotech companies than ever. Moreover, the industry is healthy and profitable.

Express Scripts is concerned by ideas that reward certain types of drug development with additional market exclusivity. Exclusivity is a marketplace incentive that perverts the commercial market for prescription drugs: it inhibits innovation; it artificially restricts competition; it affords the same reward to a breakthrough therapy as a less innovative product improvement. Moreover, it places the burden for funding this additional incentive solely on the backs of the payers of health care (employers, health plans, etc.)—rather than socialized equally by society through the tax code. Proposals that seek to expand market exclusivity in

any situation need to be approached very carefully and very narrowly to ensure it is the right solution to the underlying problem.

Chairman Pitts, Ranking Member Pallone, and other Members of the Committee, thank you for the opportunity to testify today.

Mr. PITTS. The chair thanks the gentleman. Dr. Ledley, you are recognized for 5 minutes for an opening statement.

STATEMENT OF FRED LEDLEY

Dr. LEDLEY. Good morning, Chairman Pitts, Ranking Member Pallone, members of the committee. My name is Fred Ledley. I am Director of the Center for Integration of Science and Industry at Bentley University, where we focus on studies aimed at accelerating the translation of scientific discoveries for public benefit. I have been an investigator of the Howard Hughes Medical Institute, the founder of an early company in the field of gene therapy, gene medicine, the president and CEO of another startup, which was a pioneer of personalized medicine, and I am the holder of 10 U.S. patents.

My takeaway message today is very simple, that the role of incentives should be exclusively to promote 21st century cures based on 21st century science. This requires sustained support for translational science from the early stages of basic research that comes out of the NIH through drug discovery and drug development. It requires patent rights that protect the inventor's priority to novel art. It requires predictable pricing, and it can be inhibited by statutory exclusives granted to older products, which draw resources away from the discovery of new cures and innovations that could reduce the cost of health care.

While testimony before this committee has celebrated the many advances scientific advances of recent decades, our research suggests that few of these advances are being translated into cures. Let me give you an example. Monoclonal antibodies are one of the most important classes of new medicines now covering the market but the basic science that enabled that dates to 1975. My colleague, Laura McNamee, has recently studied 100 new medicines approved by the FDA since 2010 and found that these products arose from basic science that was on average 40 years old. Thus, in the second decade of the 21st century, the pharmaceutical pipeline is not providing 21st century cures but rather cures based on 20th century science.

One reason the pharmaceutical industry is facing the dwindling pipeline and a patent cliff is that it has depended for too long on the products of old science—"me too" drugs, product extensions and the eternal hope that there will be a blockbuster around the corner. I urge the committee to focus on incentives that will move the pharmaceutical industry forward, forward from reliance on old science towards these 21st century cures.

Now, patent rights are essential for this innovation. Patents transform scientific discoveries into economic capital that can be monetized through technology transfer, capital investments by our venture colleagues, licensing fees or royalties. Innovation can be incentivized by more efficient and timely patenting of these discoveries.

Statutory exclusives can have the opposite effect. Extended exclusivity makes companies less likely to commit resources to the always risky business of translational science. Such companies are less likely to discover and develop modern cures, less likely to enter into alliances with startup companies and less likely to acquire

those companies. Extended exclusivity granted to products that are late in their lifecycle or dormant are particularly problematic since they explicitly favor the products of old science over modern science. Statutory exclusivity can promote science, as we have seen in Hatch-Waxman, in the Orphan Drug Act and in the Best practices Pharmaceuticals for Children Act, which I remind you achieved this goal with 6 months of extended exclusivity.

Even with market incentives, the path to 21st century cures needs to be nurtured. I started a gene therapy company 25 years ago. I have been working in the field for 30 years. There are no gene therapy products on the market. One of the reasons is that while more than $4 billion has been invested in gene therapy companies, all this money went to technologies that were immature and not likely to develop drugs. This is a long process that requires sustained, continuous investment. Incentives that engage stakeholders in the long-term success of innovation can promote innovation. These could include accounting standards that assign value to R&D spending, valuation models that consider the intermediate products of innovation or differential tax rates or even shareholder rights that favor long-term over short-term investments.

The reason we are here today is that the treatments and cures that were developed from 20th century science are just not good enough. There are critical unmet needs and incurable diseases and the ever-increasing cost of health care. Incremental improvements are not what we are after. I urge the committee to focus on the mission of advancing 21st century cures that move the industry forward to using 21st century science.

Thank you very much for the time.

[The prepared statement of Dr. Ledley follows:]

Statement of

Fred David Ledley, M.D.

Director, Center for Integration of Science and Industry

Professor, Natural & Applied Sciences and Management

Bentley University

Waltham, MA

Before the House of Representatives

Subcommittee on Health

of the

Committee on Energy and Commerce

Hearing: 21st Century Cures: Examining the Role of Incentives

In Advancing Treatments and Cures for Patients

June 11, 2014

Good morning Chairman Pitts, Ranking Member Pallone, and Members of the Committee. It is an honor to be here today and have the opportunity to contribute to this important discussion.

My name is Fred Ledley. I am Director of the Center for Integration of Science and Industry at Bentley University, and Professor of Natural & Applied Sciences as well as Management. I am a physician and a pediatrician, trained at Georgetown, and at Harvard and Boston Children's Hospital.

In the 1970s, I did graduate research at the National Institutes of Health and at the Food and Drug Administration, and worked with David Baltimore at MIT before beginning my own laboratory in the Howard Hughes Medical Institute at the Baylor College of Medicine. My laboratory focused on inherited diseases in children, and, in 1991, my team was one of the first to receive NIH and FDA approval for a clinical trial directed at gene therapy. In 1993, I was a founder of one of the first gene therapy companies, GeneMedicine, where we worked closely with the FDA to bring gene therapies into clinical trials, and completed an IPO in 1994. In 1996, I became President and CEO of a start-up company in the then-emerging area of personalized medicine, Variagenics, which had their IPO in 2000. I am also the inventor on ten US patents. I joined Bentley University in 2005, where my research focuses on accelerating the translation of scientific discoveries to create public value.

I am here today to share my perspectives as a physician and pediatrician, and my experience as an entrepreneur and executive in the biotechnology industry.

If I leave you with one take away message today, it is that the role of incentives should be to promote the discovery and development of 21st century cures based on 21st century science. This innovation requires sustained support for translational science, from the early stages of basic research, through drug discovery and drug development. This innovation also requires

certainty that the pricing of new products will reflect the value brought to the market, as well as incentives for entrepreneurship. Patent rights advance this agenda by protecting the inventor's priority to novel art so that it can be developed and commercialized. Statutory exclusivities granted to older products can inhibit innovation by drawing away time, talent, and resources from the discovery of new cures. I urge the Committee to focus on the mission of advancing 21st century cures with incentives that promote cures based on the science of the 21st century.

Testimony before this committee has already celebrated the tremendous scientific advances of recent decades. Research from our Center for Integration of Science and Industry, however, suggests that the dramatic scientific advances of the molecular biology era are only now being to be translated into products. In fact, most of the medicines coming to market today were discovered using basic science that is 30-40 years old.

Let me give you an example. Monoclonal antibodies are, today, an important class of new medicines with an annual market of >40 billion dollars.. The basic science that enabled discovery and development of these products was published in 1975. It was not until the 1990s, however, that a monoclonal antibody was discovered that would be developed into a successful product, and not until a quarter century after the original publication, that the first product was approved (McNamee and Ledley 2012).

My colleague, Laura McNamee, recently studied the timeline of translational science for the 100 new medicines approved by the FDA since 2010. She found that the basic science that led to the targeted discovery or development of these products occurred, on average, 40 years before these products were approved (McNamee et al., in preparation). Thus, in the second decade of the 21st century, the pharmaceutical pipeline is not providing 21st century cures, but rather cures based on 20th century science.

Over the past 40 years, basic science has advanced at an exponential, or near-exponential, pace, reminiscent of the exponential growth of computers and information technologies. We are all familiar with how the exponential advance of computers has driven down the cost of technology, while also producing dramatic new capabilities. So to, the products of exponentially advancing biomedical and pharmaceutical science have the real potential to drive down the cost of healthcare, while providing dramatically more effective cures. These are the treatments and cures that the public expects from 21st century science.

One reason the pharmaceutical industry is facing a dwindling pipeline and patent cliff is that it has depended for too long on the products of old science, me-too drugs, product line extensions, and the eternal hope of discovering a blockbuster drug (Munos 2009). Other witnesses today are addressing policies and incentives that accelerate the process of developing new medicines. I would like to focus my comments today on incentives that will move the pharmaceutical industry forward from a reliance on old science towards 21st century cures.

Patent rights are essential to promoting innovation. Patents transform nascent scientific discoveries into economic capital that can be monetized through technology transfer, investments in early-stage biotechnology companies, and licensing fees or royalties paid for rights to the invention. Patents also provide inventors with a window of opportunity to develop and commercialize their innovations. Innovation is promoted by efficient and timely patenting of scientific discoveries as well as existing mechanisms for patent term adjustments when there are delays in issuing patents, and patent term restoration when marketing time is lost in product development or regulatory review.

Statutory exclusivity can have the opposite effect. Extended exclusivity for existing drugs or biologics can create incentives for incremental innovation, making companies less likely to

commit resources to translational science; less likely to discover and develop new medicines; less likely to enter into alliances with entrepreneurial biotechnology companies; and less likely to make acquisitions of such companies. Extended exclusivity granted to products that are dormant or late in their exclusive life cycle are particularly problematic, since such policies explicitly favor the products of older science.

Statutory exclusivity can be used effectively to achieve specific social goals. The Best Pharmaceuticals for Children Act provides six months exclusivity to companies that test their products in children, and has been effective in assuring that pharmaceutical products can be used safely in children (Christensen 2012). The Orphan Drug Act, which provides extended exclusivity for products for rare diseases with limited market potential, has successfully promoted development of cures for many diseases (Melnikova 2012). The difference between these statutory extensions, and some that are proposed, is that they explicitly focus on unmet needs for which market forces provide insufficient incentive, and are limited in term.

Even with market incentives, however, the transition to 21st century cures faces an uncertain path that needs to be nurtured with strategic incentives. Let me share an example of particular personal interest; gene therapy. Recent studies demonstrate that gene therapy works, yet thirty years after basic science established the feasibility of gene therapy, there are no products on the market in the US or Europe. One reason for this lag in commercialization of gene therapy is that, while more than $4.2 billion dollars was invested in gene therapy companies between 1988 and 2012, virtually all of this investment was made in companies with immature, early-stage technologies. By the time these technologies matured to the point that they might generate effective products, investment and pharmaceutical interest had waned. In fact, UinQure, which has a product approved in Europe, Glybera, was in liquidation when approval

was granted, and was only able to attract investment, secure a corporate partnership, complete an IPO, and begin building the production facilities after the product was approved (Ledley, McNamee et al. 2013).

The problem for gene therapy, and many other, innovative cures, is that there are no mechanisms for continuous, sustained support of translational science from the first stages of basic research through drug discovery and drug development. There is a role for incentives that engage stakeholders in the long-term success of innovation. Such incentives could include accounting standards that assign value to investments in R&D (Ledley 2013), valuation models that value the intermediate products and stages of innovation (McNamee and Ledley 2013), as well as tax rates and shareholder rights (Lipton 2014) that favor long-term investments.

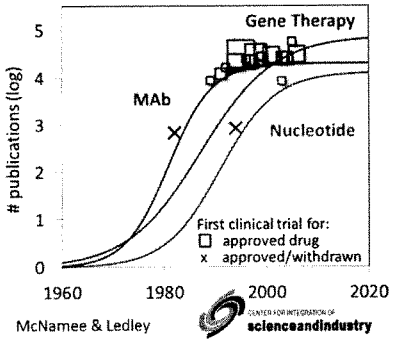
The reason we are here today is that the treatments and cures that were developed from 20th century science are not good enough; there are critical unmet needs in diseases that remain untreatable and healthcare costs that seem to be out of control. Incremental improvements or new indications for older products will not meet these needs and can be counterproductive to generating new treatments and cures from 21st century science. In closing, I urge the Committee to focus on the mission of advancing 21st century cures with incentives that move the industry forward from the products based on the science of an earlier age.

In closing, I would like to thank Chairman Pitts, Ranking Member Pallone, and Members of the Committee for the time to address you today.

NOTES

1. Timeline of monoclonal antibody development (McNamee and Ledley 2012).

The discovery of monoclonal antibody (MAb) technologies in 1975 created enormous optimism that this nascent technology would provide a pipeline of therapeutic products. The early approval of Orthoclone in 1986 reinforced this optimism, but proved to be deceptive. Over the next decade, >200 different MAbs failed in clinical trials, and Orthoclone was eventually withdrawn from the market (Smith 1996). The first successful MAb products were not approved until 1994. By 2012, there were 34 MAb products on the market and >50 in late stage trials (Reichert, Rosensweig et al. 2005; Reichert 2012).



The Technology Innovation Maturation Evaluation (TIME[tm]) model provides an analytical framework for mapping the maturation of technologies. Three biotechnologies (monoclonal antibodies, gene therapy, and nucleotide therapeutics) all exhibit S-curve patterns of maturation similar to those observed in other technology sectors. For all three, products have been successfully launched only as these technologies reach an established stage.

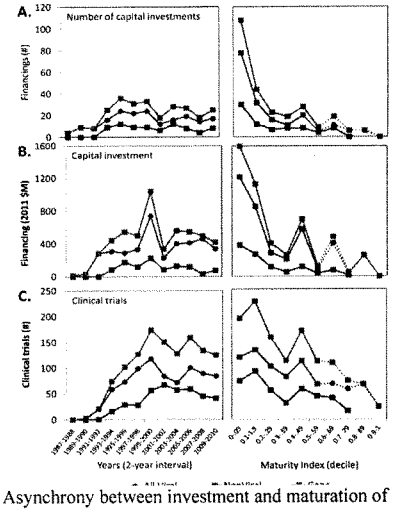
Our analysis of the MAb technology life cycle suggested that the decades of futility in clinical development corresponded to immature stages of the technology life cycle, as the field was grappling with the transition from murine MAbs to chimeric, humanized, and finally human antibodies, while also advancing screening and production methods. Consistent with observations in other technology sectors, MAbs technologies only generated successful products when the enabling technologies reached an established stage (McNamee and Ledley 2012). Since the 2012 publication, the approval of the first gene therapy (Glybera) and the nucleotide therapeutic (Kynamro) similarly correlate with the maturation of these technologies.

2. Why commercialization of gene therapy lagged (Ledley, McNamee et al. 2013)

The prospect of using DNA as a therapeutic, was recognized in the early 1970s (Friedmann and Roblin 1972; Wirth and Yla-Herttuala 2013), and was enabled by the emergence of defective viruses in the early 1980s (Mann, Mulligan et al. 1983). From 1972 to 2012 there were >35,000 research papers on gene therapy, >16,000 US patents issued that reference gene therapy, and gene therapies were investigated in >1800 clinical trials (Alexander, Ali et al. 2007; Alton 2007; Edelstein, Abedi et al. 2007). Recently, there have been a number of dramatic successes in clinical trials for diseases such as hemophilia (Nathwani, Tuddenham et al. 2011), Leber Congenital Amaurosis (Bainbridge, Smith et al. 2008; Maguire, Simonelli et al. 2008; Testa, Maguire et al. 2013), and X-linked Severe Combined Immunodeficiency (Hacein-Bey-Abina, Hauer et al. 2010) that have been heralded as the long-awaited confirmation that gene therapy can be used to safely and effectively treat human disease (Naldini 2009).

As of May 2014, however, there are no commercially available gene therapy products in the US or EU. One product, Glybera, originally developed by Amsterdam Molecular Therapeutics (AMT), received approval from the European Commission in November 2012 (Gruber 2012) after clinical trials demonstrated the safety and efficacy of this product for treating familial lipoprotein lipase deficiency (Buning 2013; Gaudet, Methot et al. 2013). AMT was in liquidation when the product was approved, and unable to launch the product. The company emerged from liquidation in 2013 as UniQure, completed a European marketing alliance with Chiesi, completed a $82M IPO in February 2014, as is currently building production facilities anticipating a launch in 2015.

Our analysis (Ledley, McNamee et al. 2013) used TIME^{TM} metrics to model the maturation of five distinct gene therapy technologies: retrovirus, adenovirus, adeno associated virus, lentivirus, and non-viral. We identified the technology focus of >50 gene therapy companies, and calculated a maturity metric (Maturity Index) for each company's technology at the time of each financing or clinical trial. The results show that over time, the number of capital investments (A, left) and total capital investment (B, left) exhibited a period of growth and then have remained relatively stable to the present time. The same data considered as a function of the Maturity Index, shows that there is a significant negative correlation between maturation and either the number of capital investments (A, right) or total capital investment (B, right). The majority of all investment in gene therapy ($5.3 billion in constant 2011 dollars) has been invested in companies with technologies that have a Maturity Index of <0.3, the level of maturity where successful monoclonal antibodies first entered clinical trials.



Asynchrony between investment and maturation of gene therapy technologies. Left panels show progression of metrics over time, shown for two year intervals. Right panels show the same data as a function of the Maturity Index, shown for deciles. A. Number of capital financings in gene therapy companies. B. Total value of capital investments in gene therapy companies (constant 2011 dollars). C. Number of clinical trials initiated. Note that not all of the ordinal technologies were mature as of the date of this analysis, so points with a Maturity Index >0.5 are shown as dotted lines.

A similar analysis of gene therapy clinical trials shows that while the number of trials has been relatively stable (C, left), a disproportionate number of trials have involved technologies with a low Maturity Index (C, right). This is significant because research in many different technology sectors has shown that early stage technologies commonly do not generate products that can meet the standards of existing markets (Foster 1986; Christensen 1997; Christensen and Raynor 2003).

3. Accounting for R&D as a fixed investment (Ledley 2013).

On July 31, 2013, the BEA announced a comprehensive revision in the calculation of the GDP, which significantly changes the contribution of R&D (BEA 2013). In the new calculation, R&D expenses will be considered a fixed investment and calculated in a new category, termed "intellectual property products." As a result, the calculated contribution of corporate profits and proprietors' income to the GDP will no longer subtract the costs of R&D as an operating expense, but only the industry-specific depreciation of R&D investments as a consumption of fixed capital (CFC). According to the BEA, these changes will provide a "better measure the effects of innovation and intangible assets on the economy."

To an entrepreneur, these changes make sense. The greatest single expense of science-driven, entrepreneurial enterprise is R&D, and the greatest asset of such companies is the intellectual property that results from this investment. In science policy, this is sometimes referred to as "scientific capital." The revised categorization of R&D ascribes a determined value to R&D investments in translational science, and recognizes the "scientific capital" that results from this investment as a positive contribution to the GDP at the time the work is performed.

The principle that R&D represents a fixed investment, as opposed to an operating expense creates a powerful incentive for investment in innovation. Accounting for R&D as an operating expense compromises earnings and profits, and negatively impact a company's near-term valuation as well as its access to capital and its cost. This is exactly the opposite effect that R&D has on long term value creation, where R&D spending may be expected to provide a significantly greater return on investment than ordinary capital. Accounting for R&D investments as a fixed investment would remove an artificial drag on corporate earnings and profits, and enhance the economic incentives for investing in innovation.

4. Valuation of biotechnology companies (McNamee and Ledley 2013)

How is the value of a biotechnology company determined? Earning-based value metrics are not relevant to research-stage companies that operate at a net loss. Moreover, such metrics systematically devalue R&D expenses of revenue-generating companies by decreasing earnings. Present value calculations can ascribe de minimis value to long-term development programs. Accounting standards that define the "fair value" of assets, including intellectual property, are heavily influenced by temporal market conditions. Most financial analysts focus on near-term fluctuations in stock price, which often reflect technical milestones, but not the steady technical progress that enables seminal milestones to be reached.

Gary Pisano (Pisano 2006) has argued that biotechnology is, at its core, a science-based business that requires distinct architecture and business models from other businesses. One critical component of such an architecture is standards for valuing science-based companies that provide for a rational appreciation of value in parallel with a company's technological successes and failures. Investors in early-stage companies should be able to invest in the strategic goals of early-stage companies with the expectation that the company's technical success towards achieving these goals will be reflected in increasing valuations. The fact that such success may not be reflected in economic metrics of value creation constitutes a systematic disincentive for investment and entrepreneurial activity in general. This is evident in the current climate of investment activity, which increasingly eschews investments in translational science, in favor of investments in products whose value can be formally measured by traditional market-based metrics. Mechanisms that credit value to the course of translational science would enable

investors to realize positive returns on investments in effective translational science and ensure that the industry continues to attract the capital required for groundbreaking research and development. For the industry to continue mobilizing the large amounts of capital investment required for translational science, there needs to be greater alignment between milestones of translational progress and measures of the value that can be realized by investors.

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Mr. PITTS. The chair thanks the gentleman and now recognizes Mr. Hemphill 5 minutes for an opening statement.

STATEMENT OF C. SCOTT HEMPHILL

Mr. HEMPHILL. Thank you. Mr. Chairman, Ranking Member, members of the subcommittee, my name is Scott Hemphill, and I am a Professor at Columbia Law School. I write and teach about innovation and competition. My research examines the incentives for drug innovation and affordable drug access provided by patents and regulation. Thank you for the opportunity to testify today about these important issues.

I think we can all agree that innovative drugs have made an enormous contribution to longer and healthier lives. Patents and regulation are the key to that success by supplying incentive to innovate, thereby justifying large investments in research and clinical testing. Patents and regulation also serve a second goal, which is to ensure low-priced access to lifesaving drugs. This is the balancing act discussed by Chairman Upton and others.

As an engine of drug innovation, of course, the patent system is not perfectly tuned. Sometimes a patent can't be secured, for example, or a drug development takes too long and the patent expires too soon.

Now, this issue is not a new problem but rather a longstanding focus of drug regulation. For example, as you have heard, the Waxman-Hatch Act fills in the gaps in patent protection by giving drugs special non-patent protection from competition, and to help make up for long development time, the Act extends the term of existing drug patents, and the Orphan Drug Act serves a similar purpose.

Now, to the extent that there is a problem even after these extra protections, the question arises, what should we do about it, and we have heard a few options. One option is to rethink and speed up clinical trials. Another is targeted public support where appropriate. A third option is to expand existing legal exclusivity. Now, the key here, I think, is to limit the expansion and target it to situations where it is truly needed, and one possibility here is Dr. Gandy's suggestion of narrower protection to help address Alzheimer's disease.

The MODDERN Cures Act also expands exclusivity but not in a way that is narrow or targeted. It would grant a large increase in protection for essentially all novel drugs. The Act gives 15 years of protection for so-called dormant therapies. Now, when I first heard the term "dormant therapy, " I figured this would be a limited, targeted expansion along the lines of the Orphan Drug Act but I think that conclusion is incorrect. The key point is that a drug must address a so-called unmet medical need but unmet medical need is defined quite broadly. It is not just a drug for a disease that has no treatment but any sort of improved outcome. So even a drug that merely improved patient compliance or increased convenience would count under the Act.

Now, in effect, the Act grants 15 years of protection to any drug with a novel active ingredient, and 15 years is a long time. It is about 3 years longer on average than even novel drugs get today, 3 years longer than biologics, and is 4 or 5 years longer than pro-

tection in Europe. The result, I fear, is a large windfall through longer exclusivity for many drugs that would have been developed anyway. Billions of dollars will be transferred from drug purchasers to drug makers, and worse, where patients pay in whole or in part for the drugs, this would also reduce access to drugs.

How big is this problem? Well, we can consider just the novel drugs that experienced generic entry over the decade between 2001 and 2010 and imagine that all of these drugs had gotten a 15-year term instead of the average 12 or so that they do today. That roughly 3-year extension would suggest an overpayment for these drugs of more than $120 billion. In other words, purchasers are likely to pay a lot more for drugs that would have been produced even without the extra protection. Beyond the windfall problem, the Act seems quite vulnerable to evergreening strategies that would extend protection beyond the 15 years, and as we have already heard, risks placing a disproportionate burden on U.S. purchasers, and I am happy to discuss these issues during the question-and-answer period.

To conclude, claims that larger drug maker rewards would increase innovation are easy to make but hard to pin down. The right next step here is careful study to determine the scope of the lost innovation problem in practice, and if warranted, a solution narrowly targeted at that problem.

Thank you again for the opportunity to discuss these important issues with the subcommittee.

[The prepared statement of Mr. Hemphill follows:]

Testimony of C. Scott Hemphill
Professor of Law
Columbia Law School

House Committee on Energy and Commerce
Subcommittee on Health

Hearing on 21st Century Cures: Examining the Role of Incentives
in Advancing Treatments and Cures for Patients

June 11, 2014

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, I am Scott Hemphill, a Professor of Law at Columbia Law School. I write and teach about the law and economics of innovation and competition. My research has considered the incentives for pharmaceutical innovation and affordable access to drugs established by patent law and drug regulation.[1] I welcome the opportunity to testify today about these issues.

Innovative new drugs have made a major contribution to longer, healthier lives. An innovator's exclusive right to market a new drug is protected by a combination of patents and regulation. This protection furnishes an incentive to innovate, thereby justifying large investments in research and clinical testing. The patent and regulatory systems also serve a second goal, which is to provide low-priced access to life-saving therapies. Robust competition from generic drugs, upon a branded drug's loss of exclusivity, is a powerful driver of lower prices. In 2013, generic drugs accounted for 86 percent of U.S. prescriptions but just 29 percent of drug expenditures.[2] Generic alternatives to branded drugs saved the U.S. health system more than $200 billion in 2012, according to an industry commissioned study.[3]

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[1] See, e.g., Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem, 81 New York University Law Review 1553 (2006); Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act, 77 Antitrust Law Journal 947 (2011) (with Mark Lemley); When Do Generics Challenge Drug Patents?, 8 Journal of Empirical Legal Studies 613 (2011) (with Bhaven Sampat); Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals, 31 Journal of Health Economics 327 (2012) (with Sampat); Drug Patents at the Supreme Court, 339 Science 1386 (2013) (with Sampat).

[2] IMS Institute for Healthcare Informatics, Medicine Use and Shifting Costs of Healthcare: A Review of the Use of Medicines in the United States in 2013, at 30, 40 (2014).

[3] Generic Pharmaceutical Association, Generic Drug Savings in the U.S. (2013).

As an engine of drug innovation, the patent and regulatory systems are not perfectly calibrated. For some innovations, the system confers a windfall. A drug maker invests in the innovation, anticipating a financial reward that is larger than the expenditure even after accounting for the risk of failure. For other innovations, the system may fail to provide a sufficient incentive. A drug maker may judge that the expected returns are not high enough, based on existing protections, and decline to pursue the opportunity. Nor is it the case that the two situations balance out. The windfalls are retained as profit, not spent on developing drugs whose expected returns fail to justify the expense.

Why might the incentive be too small? One possibility is that the drug's development takes so long that little time is left on the patent when the drug is finally approved. Moreover, for some therapies, the active ingredient might be a naturally occurring substance, previously revealed in a scientific paper, or the subject of an earlier patent, making a patent unavailable. The innovator might nevertheless secure a patent on other aspects of the drug, including the active ingredient's use in treating a particular disease. But if this or other patent protection is weak, in the sense that it is judged unlikely to hold up in court, the innovation might be discouraged. A further issue is that for innovative new uses of existing therapies, patent protection might be evaded through off-label generic use, leaving innovators with no practical remedy.

The concern that drug patent protection is inadequate—and that non-patent regulatory protection should be deployed instead—is perhaps surprising; pharmaceuticals are frequently touted as the strongest case for patent protection. But it is not new. It played an important role in the 1984 enactment of the Hatch-Waxman Act and subsequent amendments.[4] These statutes incorporate concerns about inadequate protection by providing special additional protections for drug innovators that are not available to innovators in other industries. For example:

[1] A so-called "new chemical entity" with a novel active ingredient receives five years of regulatory protection from generic competition, after which a generic firm may file paperwork in support of its bid to enter.[5] That process takes some time, so in practice, protection lasts for six or more years.

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[4] This testimony focuses on the legal regime for drugs that are chemically synthesized. A full analysis would also examine biologic medicines derived from living sources, which are subject to a different legal regime.

[5] 21 U.S.C. § 355(j)(5)(F)(ii). If a would-be generic entrant challenges one or more branded patents, it may file the paperwork after four years.

[2] If the drug is backed by a patent—even a weak patent—the protection is usually longer, thanks to an automatic stay of generic drug approval while the branded firm sues the generic firm for patent infringement.[6]

[3] Special patent extensions partially compensate for the time spent in clinical trials and the post-trial FDA approval process.[7]

[4] Exclusivity—both regulatory and patent—is extended by six months if the drug maker performs tests to evaluate the drug's pediatric health benefits.[8]

[5] Under the Orphan Drug Act, drugs treating "rare diseases or conditions" receive a seven-year exclusivity period.[9]

[6] The first generic firm to challenge a branded drug's patents is eligible for a 180-day exclusive right to market in competition with the branded firm, before other generic firms may enter.[10] This exclusivity protects the first-filing generic drug maker from entry by other generic firms, and confers a collateral benefit on branded firms by protecting against additional generic challengers until the 180 days have expired.

These additional protections have frequently proved beneficial to innovators in the course of developing new drugs, particularly drugs in which patent protection is otherwise too brief or too weak.

Even with these industry-specific increases in exclusivity, it is likely that some drugs are not developed by drug makers because the rewards are not large enough. The size of this problem in practice is unclear. Assessing the extent of "lost innovation" in the pharmaceutical or any other industry poses a difficult empirical challenge. One careful recent study focuses on clinical trials for cancer, showing that drugs to treat patients with long survival times are disadvantaged by the current system, because the clinical trials are longer, resulting in shorter exclusivity.[11] One question, to which the answer is currently unclear, is whether long clinical trials in general are correlated with more important innovation. Overall, there is a great need

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[6] Id. § 355(j)(5)(B)(iii).

[7] 35 U.S.C. § 156.

[8] 21 U.S.C. § 355a.

[9] Id. §§ 360cc.

[10] Id. § 355(j)(5)(B)(iv).

[11] Eric Budish, Benjamin N. Roin & Heidi Williams, Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials (working paper 2013).

for a careful empirical evaluation of the incentives of drug makers, including work that takes an independent look at the internal metrics that drug makers use to assess projects.

To the extent that long clinical trials pose a threat of lost innovation, one option is to alter the structure of trials, by using surrogate endpoints rather than measures of survival, a change that would permit a shorter trial.[12] Another is to fund the trial through a targeted government subsidy, rather than post-approval exclusivity. A third option is a tailored increase in post-approval exclusivity, limited to those types of innovation where the underproduction problem is important.

Section 201 of the MODDERN Cures Act takes a different tack.[13] It offers a large increase in protection for all novel drugs. In particular, it provides a 15-year regulatory term of protection to "dormant therapies" with a novel active ingredient. That term might be taken to suggest a limited scope of application, along the lines of the Orphan Drug Act. But in fact "dormant therapy" is a misnomer. Virtually any drug with a novel active ingredient would receive protection. The key requirement is that a drug must address an "unmet medical need."[14] For example, a disease for which no therapy exists would count.[15] But the standard is extremely elastic, sweeping in drugs that offer a wide range of improved outcomes, different side effects, or even increased "compliance or convenience."[16] It is hard to think of a new chemical entity that would fail this test.

In effect, section 201 extends regulatory protection for new drugs to 15 years. Fifteen years is several years longer than the existing overall protection for most new drugs. In a previous academic study, Bhaven Sampat and I examined a set of 117 drugs with a novel active ingredient that experienced generic entry during the decade between 2001 and 2010.[17] The average (mean) market life for the branded drugs was 12.2 years. The proposed protection is also three years longer than the 12-year data protection for new biologics. It is longer than 10-year (which may be extended to 11-year) data protection in Europe.

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[12] Id. at 15-16.

[13] H.R. 3116, 113th Cong. (2013).

[14] Id. § 201(a)(2)(A).

[15] Id. § 201(i)(1)(A).

[16] Id. § 201(i)(1)(B).

[17] Hemphill and Sampat (2012), *supra*. The paper analyzes 119 drugs with at least one Orange Book-listed patent. Six drugs with no patent protection are omitted. The analysis in the paper includes two drugs that were denied new chemical entity protection because each contained a previously approved active ingredient. Those two drugs have been dropped from the present analysis.

Section 201 would thus grant a windfall for a large number of drugs that would have been developed anyway. As to these drugs, the effect is to transfer money from drug purchasers to branded drug makers. To the extent that patients pay in whole or part for drugs, this provision would also reduce access to existing drugs. Apparently recognizing this issue, an earlier version of the bill made a modest effort to cabin its effect by requiring a showing of "prospectively insufficient patent protection."[18] The provision was quite limited in effect, merely requiring a certification that anticipated post-approval patent protection was less than 14 years. But even that limited provision has been removed from the current bill.

The resulting windfall would be quite large. To obtain a rough estimate, we can examine the 117 drugs discussed above. If all of these drugs were protected instead by a 15-year regulatory term, most would enjoy a multiyear extension of protection; a few would have shorter protection. Taking into account the sales of each drug, a back-of-the-envelope calculation suggests that the switch would transfer $121 billion from purchasers over the course of a decade.[19]

This calculation assumes that all drug makers switch to a 15-year term. If, to the contrary, a drug maker is able to predict when its protection will be longer than 15 years—in other words, when opting into the MODDERN Cures Act would offer less protection than the status quo—it will opt out. In that case, the total transfer would be even larger.[20]

There is a second problem. Fifteen years is likely to serve as a floor, not a ceiling. The 15-year regime appears to be subject to manipulation that has the effect of extending exclusivity. One form of manipulation, to which the MODDERN Cures Act appears particularly vulnerable, is "product hopping." At the end of a branded drug's exclusivity, a branded firm has an incentive to shift patients and doctors to a line extension before generic entry occurs. This shift can be accomplished by promoting the new product, increasing the relative price of the old product, or withdrawing the old product from the market. An example is Namenda, a treatment for

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[18] H.R. 3497, 112th Cong. § 201(b)(2)(C), (d)(1) (2011).

[19] The average per-drug increase in branded sales is $2.06 billion (in 2010 dollars), under the assumption that drug sales remain at the same level during the extension or reduction, compared to the benchmark year prior to generic entry, rather than increasing or falling off. Assume further that generic competition would save purchasers one-half of the branded price. Finally, ignore discounting. Applying these assumptions yields a total transfer of $121 billion (= $2.06 billion x 1/2 x 117 drugs) over a decade. This calculation does not include welfare losses caused by price distortions.

[20] For example, 16 drugs in the Hemphill/Sampat sample had a period of exclusivity greater than 15 years. Suppose that the makers of these drugs opted out, and the remaining 101 drugs switched to the 15-year term. In that case, the average per-drug increase is $2.5 billion. Using the same assumptions introduced in footnote 19 yields a total transfer of $126 billion.

Alzheimer's disease. The drug maker has announced that in August 2014, it will discontinue Namenda tablets, thereby assisting its push to switch patients to a newer once-a-day formulation with stronger patent protection. Patients who are doing well with the tablets, and who could otherwise take advantage of a cheaper generic when exclusivity ends in 2015, are deprived of that choice. The absence of protection against product hopping and other tactics would likely extend protection under the MODDERN Cures Act well beyond 15 years.

Finally, the burden of this proposal falls entirely on the shoulders of U.S. purchasers. One consequence is that a particular increase in U.S. exclusivity has a less-than-proportionate effect on drug maker rewards (and hence a lesser effect on incentives), to the extent that the increase occurs in the United States alone. Moreover, U.S. purchasers already bear the greatest part of the burden, through higher drug prices, in supporting innovation that has a global benefit. A further increase in U.S. protection would tend to exacerbate that disparity.

* * *

Claims that larger drug maker rewards would increase innovation are easy to make, but hard to pin down. The right next step is careful study to determine the scope of the lost innovation problem in practice, and if warranted, a solution narrowly targeted at the problem. Targeted solutions that do not confer a windfall include modifications to trial protocols and government support of long-lasting trials where appropriate. Special increases in exclusivity should be narrowly tailored, a concern reflected in the Hatch-Waxman Act and Orphan Drug Act, but missing from the MODDERN Cures Act, which would cost purchasers many billions of dollars in higher prices for drugs that do not require any additional incentive to elicit. Thank you for the opportunity to discuss these issues with the Subcommittee.

Mr. PITTS. The chair thanks the gentleman, and that concludes the opening statements of our panel.

I would like to ask unanimous consent to submit for the record a statement submitted by the Premier Health Care Alliance and a statement submitted by the Generic Pharmaceutical Association. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. We will now begin questioning, and I will recognize myself 5 minutes for that purpose.

In a statement issued by the California Public Employees Retirement System related to this hearing, they state that "Despite historic breakthroughs in scientific research, clinical trials and new lifesaving therapies, many common diseases remain incurable. Heart disease and stroke continue to be leading causes of mortality. Psychiatric diseases are serious burden on patients, their families and society as a whole, and infectious disease presents new critical challenges in terms of drug resistance."

I will note that the committee acted in an overwhelmingly bipartisan manner to pass the GAIN Act as part of FDASIA, which was a needed first step towards addressing this innovation gap by granting an additional 5 years of exclusivity to new qualified infectious-disease products. We must build on this momentum in the antibiotic space as well as in other areas of unmet medical need and where public health demands innovation.

We will start with you, Mr. Borisy. Have there been breakthroughs in clinical trial designs for chronic diseases that impact large patient populations?

Mr. BORISY. So we have seen—if the goal is ultimately to get medicines to patients and to our society that needs them, we have seen through breakthrough therapy, through accelerated approvals in multiple different disease areas an adoption of approaches that have helped to speed those therapies to the patients that need them. So it becomes a question of, what is the information that is necessary to understand how a drug will be in the real world setting and are we applying the current best understanding of biomarkers, of personalized medicine subsets of patients in some of these other disease settings, could we move things more quickly.

Mr. PITTS. How long does it typically take to conduct a clinical trial for a new therapy targeting a chronic condition such as heart disease or stroke?

Mr. BORISY. The total time in clinical development for those types of chronic diseases are usually longer than 10-plus years.

Mr. PITTS. Are venture capitalists investing in the development of new products targeting chronic diseases?

Mr. BORISY. It is very difficult to do so. If our focus is on patients and bringing through those innovative breakthrough medicines, if the time in clinical development is going to be on the order of 10-plus years, building from wonderful basic research that has been done, there still is usually additional years before you ever get to the clinic to create that drug that can then go be in the clinic for another 10 years of development. So as a venture capitalist, if you are considering deployment into an area that is going to take 15-plus years before it may get to the market, that is very challenging. It is challenging in that time period is longer than the length of

our investment funds, which means that we will be dependent on other entities, recognizing that that is an important product for patients, but other entities, if they have uncertainty about how long it will take them to continue developing it or what risks may be involved, we will not recognize the value that we have created early on. So that long period of time and uncertainty makes those very conditions which as a society and as a Nation we need to be some of the most challenging to invest in from a venture-capital perspective.

Mr. PITTS. Thank you.

Dr. Gandy, in your testimony you note that the lack of therapeutics for chronic conditions such as Alzheimer's places an enormous strain on our country's finances and that without novel therapies, costs will only escalate. At this rate, will the next generation of Americans that develop Alzheimer's be taking the same medications that were approved over a decade ago, and what would this mean to health system costs?

Dr. GANDY. At this point, the medications that are used to treat Alzheimer's disease are the same that were developed in the 1970s, so we have nothing new on the horizon. Those medications don't change the progression of a disease. They relieve symptoms briefly. They always wear off. So we continue in the current cycle of having no way to slow the progression of the disease.

Mr. PITTS. And Mr. Boutin, the California Public Employees Retirement System asserts in their testimony that the market exclusivity period of 5 years for brand drugs is "appropriate to properly incent innovation." Can you comment on whether 5 years of exclusivity is appropriate to properly incent innovation for chronic diseases?

Mr. BOUTIN. It is clear when you look at the number of conditions that lack treatments that it is not. It has worked in some cases but we now have approximately 7,500 conditions without treatments, and I hear Representative Waxman's comment of "the science is not always there" but the incentives are clearly not there to drive the innovation we need for many of the conditions. We hear from NIH-funded researchers that they develop treatments or potential treatments that could come to market but lack patent protection and therefore they don't. We hear repeatedly from our patient organizations and the organizations they work with on developing treatments that the timeline is taking too long to bring many of these products to market. We have a huge opportunity to incentivize them.

Now, I think the question is, what is the right balance point of incentivizing them. I think we agree that the need is there, and I want to just take issue with the notion of unmet medical need. Unmet medical need is really important to people with chronic conditions. Alzheimer's is clearly an unmet medical need but so is ALS, so are countless other conditions without effective treatments. Our challenge is to incentivize those highly innovative, highly valued products to address those needs. We can quibble over what that balance is but this Congress has an opportunity to do the hard work, figure that out and incentivize treatments for people who are dying now waiting for them.

Mr. PITTS. The chair thanks the gentleman. My time is expired. The chair recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask some questions of Dr. Gandy and Dr. Miller. Let us start with Dr. Gandy.

In reading your testimony, it is apparent that you share my concern about the seemingly ever increasing cost of drugs and its impact on both patients and on the health care system as a whole. You mentioned the Affordable Care Act and the biosimilars provision, which provided for 12 years of exclusivity for innovator biologics, and as you point out, biologics are extremely expensive, 22 times the cost of ordinary drugs, so if a biologic at that price were to be discovered for Alzheimer's, it would cost as much, if not more, than it currently costs to treat and care for patients with the disease. It would also not alter the unsustainable trajectory for Medicare as your testimony explains.

You mention an Alzheimer's Association report that concluded that if there were an effective Alzheimer's treatment that could delay the onset for 5 years, American taxpayers would save $447 billion in the year 2050 and the human suffering brought by Alzheimer's of course heartbreaking and obviously the projections for how much of our health care system will be spending on the care of those with Alzheimer's are dire. So it would be a tremendous public health advance if we could get this treatment and see that kind of savings, and I share your goal in trying to bring this treatment to market. Your recommendation to the committee is that we would consider extending the current 5-year term of exclusivity for drugs to treat Alzheimer's but I seriously question whether a lengthy exclusivity will achieve the kind of savings we all hope to see or whether it would necessarily give patients access to treatments they can afford, and your testimony seems to assume that if we extend exclusivity for traditional or small-molecule Alzheimer's drugs, the price of these drugs would be lower than we are seeing in the biosimilars area. I think we have seen recently that is not a safe assumption to make, and your testimony points out that ideally a novel Alzheimer's treatment would start to be given to people in their 50s before they develop symptoms in order to slow the development of plaques.

So Dr. Gandy, if we are talking about giving a drug that could actually prevent Alzheimer's, how many people do you estimate would need to take it? Obviously the dosage might take different forms. If it is an oral solid, I would guess that it might need to be taken daily, maybe even more than once a day, and that potentially means taking a drug every day for decades. So I guess I wanted to ask, if we were talking about that kind of drug, how many people do you estimate would need to take it? I just have to ask a series of questions, if you could.

Dr. GANDY. Sure. The number of people who would have to take the medication would be in the tens of millions.

Mr. PALLONE. And what if the cost of this new Alzheimer's treatment was $1,000 per pill, and if we extended the term of exclusivity for that treatment beyond the current 5 years to, say, 12 years, as you suggest, or even 15 as some of my colleagues suggest,

what would that look like for an individual patient and what would it look like for the health care system overall?

Dr. GANDY. I think the details of how to focus the exclusivity and target it narrowly are sort of a second-generation problem. I mean, I think we are really trying to find ways to deal with what we clearly observe as the retreat of the pharmaceutical industry from Alzheimer's both at the venture level and at the large pharmaceutical level, and this is at least a way to begin to do that, but I share your concern about the expense, and it is difficult to know exactly which business model to use to get started. But think of the financial savings from the polio vaccine, think of having people who would be on iron lungs for their entire lives. There clearly needs to be some balance between the exclusivity and the cost savings.

Mr. PALLONE. Well, let me ask Dr. Miller. Would you comment on it? Would you care to comment?

Dr. MILLER. Yes. I am very familiar with Alzheimer's. I am on the board of an Alzheimer's cure at the University of California San Francisco and so have studied this quite a bit. It turns out these models of savings often are never seen in reality so it doesn't matter if you are looking at drugs, devices, imaging or even robotic surgery, they often have these models when they try to get to the marketplace but their savings are rarely appreciated when they get to the market, therefore, the health crisis we have today.

If you look at this drug, though, and you were to take your scenario, you just make it the price of a traditional oral solid branded product, you would quickly actually mitigate if not swamp any potential savings that are there, especially when you consider drug price inflation. That model that you are speaking to prices the new therapy at zero. It is free. And so the savings of a half trillion dollars or when the drug is free. If you have to truly treat the tens of millions that you are talking about, you would never have any savings.

Mr. PALLONE. And the problem I have is if we grant exclusivity, we are essentially giving the pharmaceutical free rein to charge whatever it wants during that time period, and we are removing the effect of market competition forces, and I don't think we have any guarantees that a company developing a new groundbreaking drug treatment would do the same thing and obviously that is my concern.

Dr. MILLER. Well, it has been our experience that they don't because they do have the ability to freely price in the United States, and if you are going to treat Alzheimer's, there is a lot of reasons to treat Alzheimer's. This is not about an economic argument. This is because it is the right thing to do for patients, but the likelihood of us seeing savings downstream are much less likely, especially if you extend exclusivity.

Mr. PALLONE. Thank you very much. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognize the chairman of the full committee, Mr. Upton, 5 minutes for questions.

Mr. UPTON. Well, again, we appreciate all your testimony this morning.

Mr. Carusi, the fact that the number of venture capital firms investing in medical technology has dropped from 39 in 2007 to just

about 11 or 12 today is certainly concerning to a lot of folks. Who is going to provide the necessary startup capital for innovative new medical technology companies? How can we grow that number back to where it was before?

Mr. CARUSI. Well, I think that is exactly the challenge right now. I think at its core, venture capitalists raise money from institutional investors, so we raise capital from universities, endowments, pension funds. As a part of that process, we also have a fiduciary duty to generate returns. That is the agreement that we are entering into. We can get that number back to 20, 25, 30, 35 if we can fix the math problem that we have, which is that it is very difficult right now to generate the kind of returns that our investors need to see when you look at the delays of FDA, you look at the delays of reimbursement. So I think this Congress and we as a device community, if we can find ways to get back to streamlining that innovation process, the math starts to work better and that starts to bring these investors back into the fold. Until then, we have been forced to go elsewhere, and as we like to say, we have been looking for a new set of best friends. That is in part why I am spending a lot of time my time overseas, and so we have seen other countries that are very interested in building their own life sciences ecosystem invest in venture capital funds directly in return for us locating our companies in those local geographies. So there are ways to access capital but it does come with strings and some of those strings are that we need to start to conduct business outside of the United States, and we are doing that right now to fill the gap.

Mr. UPTON. So are those venture capital companies that are helping companies overseas, are they located overseas themselves or are they U.S. firms that are investing and then encouraging those companies to in fact develop those products overseas?

Mr. CARUSI. So will speak for my own firm. Our new fund, Lightstone Ventures, it is a U.S.-based fund but we are—in fact, we just announced that we are opening an office in Dublin. We are moving one of our partners to Dublin, and a part of what we will do, not all, but a part of what we will do will be to look for innovative ideas and innovative technologies but to reside those companies overseas and to build those companies overseas. And so they are U.S. funds that are locating elsewhere.

Mr. UPTON. Is any part of that equation that decision making part of the tax code consequences? I know we lost a company in my district to Ireland—Perrigo—in terms of their headquarters, in large part because of the tax rate of 35 versus 10 ½.

Mr. CARUSI. So that has certainly been in the press and certainly tax rates and lower tax rates and more attractive tax rates play a role but recognize the fact that our companies are very far from revenues and very far from profits and so the bigger driver for our companies is really around, A, the access to capital, and B, the regulatory environment in those markets, and it comes back to the fact that we can get a device product approved in Europe 3 to 4 to 5 years ahead of what we can get that product approved in the United States. The fact that product is approved 3 to 4 to 5 years ahead of time then allows us to start to do the studies that the payers want to see to start to try to generate some of the cost data.

In the United States, we are behind in that cadence and so consequently given the fact that we are now running these trials in Europe and seeking European approval, we like to be close to our companies. We don't just invest and so we are naturally moving overseas to be closer.

Mr. UPTON. Mr. Borisy, you referenced the expected patent life and market exclusivity of a drug in development does impact the investment decisions, and you also indicated earlier that the size and cost of clinical trials is an impediment to investment and innovation. What are other thoughts that you might have in advancements and technology that can help make up the difference for those?

Mr. BORISY. So for any drug that is being brought forward, as a society we are putting a level to say what is the information that we need to have that drug will be useful in the real world population and make a difference for patients and have the requisite safety information associated with it. We have in areas as has been discussed here in the committee in cancer and rare genetic diseases been willing to adopt the use of biomarkers, surrogate endpoints, and a recognition that the full understanding of the use of that drug will come post approval with experience in the real world.

For some of these areas that are outside of cancer and rare genetic disease, there are likewise opportunities to take some of those modern approaches, and we can be doing that both pre approval as well as post approval. I think an important point to recognize is to the comment of we are in the 21st century now and not the 20th century with electronic medical records, with information technology, we are able to know an enormous amount about what is actually happening with a drug in the real world. So when we are dealing with the question of how do we develop drugs for some of these chronic diseases, some of these things affecting such large swaths of our population and we are dealing with the question of how do we make sure that innovation invests in those areas. We should ask, can we use some of these modern technologies to make that process more doable, more stable, more predictable.

Mr. PITTS. The chair thanks the gentleman and now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you very much, Mr. Chairman. I appreciate all the testimony. I am sorry, I had to go to another subcommittee and didn't hear all of your oral presentations. The chairman has often said to me, I ought to clone myself, but we don't know how to do that, and it probably wouldn't be allowed anyway, and nobody would want it.

Mr. Hemphill, I want to ask you some questions about this MODDERN Cures Act, because that is a legislative proposal that has been put forward. In your testimony, you said it is likely that some drugs are not developed because the exclusivity rewards are not large enough, but it is unclear how large a problem this is, and I would like to explore that with you. Certainly we ought to be willing to use patent term extensions and exclusivities as an incentive to spur the research and development of new drugs. That was the basis of some of the laws that we are all praising like the Orphan Drug Act. In that law, we gave 7 years of market exclusivity for

drugs to treat rare disease. That meant that these were rare and didn't offer a huge profit potential because they weren't a lot of people that were likely to buy the drug but this MODDERN Cures Act gives not 7 but 15 years of exclusivity and post-approval patent protection to so-called dormant therapies. Do you see a reason why we would need an even longer period for these drugs than we gave for orphan drugs? The Orphan Drug Act has been very successful. We have a lot of new drugs for people with these rare diseases.

Mr. HEMPHILL. So I would say no, not necessary under the MODDERN Cures Act as it is currently conceived, given the breadth of applications of unmet medical need and its applicability to essentially any new drug. I leave open the possibility that in principle, there could be therapies for which the lead time is so long that some kind of targeted additional protection would be worthwhile. I just think the MODDERN Cures Act goes way beyond that in its current breadth of application as well as its duration.

Mr. WAXMAN. In a biosimilars provision in the Affordable Care Act, we gave 12 years of exclusivity to biologics. That is 7 years longer than we gave in Hatch-Waxman for small-molecule drugs. I have always believed that the 7 years was too long. However, the argument was made that a lengthier time was needed because biologics were harder to develop and their patents were weaker. Do you see any reason why dormant therapies would need 3 years longer exclusivity than biologics?

Mr. HEMPHILL. Well, I think in principle, it is always possible that longer protection would elicit additional innovation, and then the question is, at what cost to the therapies that we would get either way, which is why I think it is so important for us to do careful study to figure out where those gaps are, if anywhere.

Mr. WAXMAN. Well, you mentioned the evergreening provision in your testimony. Now, that is not just a one-time event, that could go on forever wherever a small change can produce another 15 years of exclusivity. There was an interesting statement. Mr. Boutin in his testimony claims that MODDERN Cures has the strongest anti-evergreening language ever included in legislation. Do you agree with that? Do you think that that law prevents evergreening or could companies get multiple 15 years exclusivity?

Mr. HEMPHILL. I don't agree. I am very concerned about evergreening in this bill. There may be a difference in what we mean by "evergreening. " One particular issue that I am very concerned about is product hopping where you get close to the end of the exclusivity and then the drug maker switches the patients over to a new version of the same drug. We have been talking about Alzheimer's, and Namenda is a nice example. The existing Namenda treatment is going away this summer and all the customers are being—all the patients are being shifted to a once-a-day version, and this extends the exclusivity, and I don't see how the MODDERN Cures Act is going to get around that.

Mr. WAXMAN. This MODDERN Cures proposal, the sponsors point out it is only for therapies that address an unmet medical need for serious or life-threatening diseases. On the surface, that sounds reasonable. Do you think it is appropriately targeted to only those drugs whose development would warrant and be appro-

priately stimulated by such extraordinarily long periods of exclusivity and patent protection?

Mr. HEMPHILL. It looks like it would apply to roughly any drug that currently gets new chemical entity protection. Maybe there are small exceptions to that but I think it extends quite a bit further than what would you normally think of by unmet medical needs.

Mr. WAXMAN. And that could be a huge windfall?

Mr. HEMPHILL. Correct.

Mr. WAXMAN. Mr. Boutin, I know you met with our staff on several occasions, and I understand you are trying to get them data and information to show whether there are significant numbers of dormant therapies out there waiting to be developed. Have you had any success in collecting this data? And I would also appreciate data justifying why 15 years of exclusivity and patent protection are necessary for these therapies.

Mr. BOUTIN. So with respect to the data question, there is data that is available but it is very limited. It is very challenging to collect that information because the incentives are not there to exist, and when we speak with companies, they routinely tell us that when they had a good product that they shelve because it has gone dormant because there is not enough time to develop it, they routinely shred the data. What we have seen with the filing of MODDERN Cures is, companies now are starting to keep that data in-house. So they are starting to look at how they might potentially recapture these lost opportunities.

Mr. WAXMAN. Well, it is important that we insist on receiving more information as we look at this law because this is a huge windfall in some cases, and we want to know if it is necessary. If it is necessary, we certainly want to do what will help spur innovation.

Mr. BOUTIN. Well, in——

Mr. WAXMAN. But we know, Mr. Chairman, in conclusion, that there have been many laws where we have just overpaid. We have overpaid the drug companies to do research on dosages for kids and we look at how much money that costs them to do it and that exclusivity was so much more valuable. We have overpaid for even some of the orphan drug laws, and we are overpaying at the expense of patients going without drugs or the payers for drugs not being able to afford it or the Medicare system and the Affordable Care Act not being able to sustain these kinds of costs. So we have got to get the balance right and we need the data to make sure that we are doing that. Thank you.

Mr. PITTS. The gentleman's time is expired. The chair now recognizes the vice chair of the committee, Ms. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman, and I want to thank everybody for being here and we have a hearing downstairs as well as here so we are kind of back and forth.

Mr. Carusi, I want to come to you. I would like to talk with you a little bit about your due diligence process as you look at funding a startup with a concept, and being from the Nashville area where a lot of health IT is taking place and Health Box is active there, the Entrepreneur Center, when I go over there and I talk to some of these innovators and you look at what is taking place from con-

cept to commercialization to distribution, it is a pretty long timeline. In preparing for the hearing and reading through your testimony, I want you to just talk to me about that due diligence process, what you are looking at, how the FDA approval process affects that, how that window has changed in the past 10 to 15 years.

Mr. CARUSI. I would be happy to. I think it is important to note that at my firm, so at Lightstone, we are involved from the very early stages. In fact, about a third of our companies have been created either in-house or in coordination with incubators that we work with. So this means that we are literally sitting down with an entrepreneur, a physician, an inventor looking at a market and inventing. So we are involved at that early stage. We then have to take a look at that starting process. We have to look at the technical risks, the development risks, the risks in the clinical trials, what kind of a study can we run. If we run that study, will we get FDA approval. How long will that take. We then have to make a determination as to whether or not we will have created enough value that we can then find another player, be it at the public market or one of the major players take on that project or if we have to keep going. If we have to keep going, then we have to look at the whole reimbursement process, what is involved in getting coding, coverage, payment. At the end of the day, we have to get the product from the ideation phase all the way through to the point where we are generating revenues and we are generating profits. That is what we do. If you look at that timeline, and Mr. Borisy has already mentioned this, that timeline is now pushing anywhere in devices up to 8 to 10 to 12 years with a great deal of uncertainty along the way, and one of the things that we as venture investors hate the absolute most is seeing our companies fail late. We would rather introduce experiments where we can have these companies fail early and move on. But what is happening is, these companies are either failing at the point where they get in front of panel for FDA approval, even if we have met the appropriate endpoint, or they are failing when they get into the morass of reimbursement, and then they become restarts. Nobody wants to fund a restart. It is easier to give birth than resurrect, and the reality is, if these companies then die and we have to move on and it is dragging won the returns of our industry and it is dragging down innovation, and that is the process that we are facing right now.

Mrs. BLACKBURN. You mentioned the challenges with the IDE process. Do you want to add anything more to that?

Mr. CARUSI. Yes. So I mean, again, on the IDE process, that is the process to actually initiate our clinical studies to then demonstrate the safety and the efficacy of the device. What happened over the years is the data requirements to start those studies, it was as if we were actually going for approval. We are not going for approval; we are going for the approval to start the trial. And again, some of these are going to fail. They are not going to work. If you start to layer on additional preclinical requirements, additional bench requirements that aren't necessarily adding to the safety of these products, then again you are adding to the cost of time before we actually get to the experiment where we can run the clinical trial and see if the product is safe, more effective and

good for patients, and if it costs too much, capital is fungible. We will go somewhere else.

There was just a discussion around Alzheimer's. We are not funding Alzheimer's drugs. We can't. We can't bring them to market. And so the math won't work, and so it is simply a matter of making sure that the right incentives are in place so that we don't kill innovation. At the same time, we are in the game of disrupting things. That is what we do for a living. So we don't want to see incumbents sitting on drugs and new devices down the road but we need enough incentive to make sure that the math works so that we can fund them to begin with, and right now in a lot of spaces, we are not able to do that.

Mrs. BLACKBURN. Thank you, and I will yield back my time, Mr. Chairman.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the gentleman, Mr. Matheson, 5 minutes for questions.

Mr. MATHESON. Thank you, Mr. Chairman.

I want to talk a little bit about the issue with medical devices, small manufacturers in particular. They are the ones in the marketplace who are really creating some of the groundbreaking technologies. They rely heavily on venture capital, as we just heard in the last answer. And I think that as should be expected, venture capitalists are going to only take on a certain amount of risk both in terms of product performance and uncertainty and regulatory uncertainty as well because uncertainty in business is a cost. I think that sounds pretty basic but I think that is something Members of Congress need to be reminded of.

One area in which I believe venture capital firms consider when deciding whether to make an investment in medical device is the likelihood of adequate and predictable reimbursement from Medicare because once you get FDA approval, that doesn't mean Medicare is going to give you reimbursement.

Over the past several years, I have heard from device manufacturers and venture capital firms that Medicare is requiring more data to obtain appropriate coverage of payment, and I appreciate that CMS wants to put forth an effort to spend taxpayers' dollars in an efficient and responsible manner, but this change in standards, if you will, and the lack of clarity surrounding what the standards are from what I understand has made it increasingly difficult for VC firms to make an educated and informed decision about the viability of a device once it gets through the FDA approval process. So if an FDA-approved device is not approved by Medicare, its viability in the marketplace and the ability for patients to access the technology obviously is greatly reduced.

In order to help alleviate some of this uncertainty, I have cosponsored legislation authored by my friend and colleague, Congressman Paulson, the Accelerating Innovation in Medicine, or AIM Act, which would give device manufacturers the opportunity to make an FDA-approved product available on a self-pay basis for an initial 3-year period before approaching CMS about Medicare coverage on reimbursement. This program would be entirely voluntary. It would allow manufacturers the time to collect needed data to justify reasonable and adequate coverage and payment for Medicare down the road, reducing some of the uncertainty associated with

the Medicare coverage process and hopefully providing the venture capital community with a measure of certainty in the device and more broadly in the market in general.

So Mr. Carusi, I wanted to ask you if you had heard of this or were aware of this proposal and do you feel it would assist both the venture capital community and the small device manufacturers in reducing some of the uncertainty in the process and bringing products to the market on a more expedited basis?

Mr. CARUSI. Yes, I am familiar with the AIM Act, and I think it very much goes to the heart of one of the challenges that we are facing, which is to your point. We now have FDA approval but we are now in a process where we have to generate more data. As we are generating that data, we are not profitable entities. We are burning $500,000 to $2 million a month, and in fact, that number tends to go up because we now have to start marketing these products. So the question comes down to, we can't as small companies continue to fund these products through that next phase of development. So I think what the AIM Act does or could potentially do is help to provide a source of funding during this period of time so that we can continue to generate the data that payers, that Medicare would want to see.

Look, the world has changed. We recognize that data is everything. Clinical data is our sole focus, so generating that data is necessary, it is important, but if we are going to have to add more years, more uncertainty and more disruption, then we need policies like the AIM Act, and I would say that is one of several potential approaches. That is not going to do it. We need more things and more creative ways to try and think about how we can as an ecosystem help the ecosystem generate this data. It is not simply about device companies or biotech companies. It benefits hospitals, payers, patients. So what is the right mechanism to fund this additional data-gathering exercise?

And then the other thing I would add is, and then what is the data that is required. Don't move the bar. Tell us—and we have had this conversation with FDA. If it is X, we hit X, then you are going to get paid, and right now that bar is constantly moving so we don't even know if we generate that data if we are going to get payment and coverage.

Mr. MATHESON. I appreciate that.

Mr. Chairman, I will yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes the vice chair of the subcommittee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman, and Mr. Carusi, just briefly before we leave that point, it was the intention or the desire of this committee 2 years ago when the reauthorization of the Food and Drug Administration came to our committee that many of these problems would be, if not solved, at least managed or mitigated, and that has not been the case?

Mr. CARUSI. No. On FDA, that is having an impact, and so I think we are starting to see benefits from FDASIA, and certainly with FDA and improved dialog with Commissioner Shuren and his leadership, we are seeing improvements. So that is why in my testimony I moved from FDA, we still want to continue to improve it,

but to the reimbursement side of the equation because parallel to the discussions we had several years ago around FDA and a lack of transparency and predictability and consistency, that is what we are now facing in reimbursement.

Mr. BURGESS. Let me ask you a question because it came up yesterday in a Rules Committee hearing over the appropriation for the United States Department of Agriculture, which for reasons that escape most of us includes the FDA. But the whole issue of special protocol assessments came up and the fact that the rules might be changed late in the game in that environment. Can you speak to that just briefly?

Mr. CARUSI. Yes, I can. Again, I think that has been utilized more on the drug side, which is frankly less where I play. It is probably more where you play. Again, I think the intention of SPAs is terrific. I think the intention is to provide again a bar where if you hit a certain data requirement, you have certainty that you will get approval. That is the right intent. Where it runs into problems if that doesn't prove to be the case. So in other words, if you are now three-fourths down the process, you are in the middle of your clinical trial and the bar has changed, the bar has moved, you have to start that clinical trial all over. You have just taken a step of 3 to 4 years back. In many ways you may have flushed $50 to $100 million down the drain. So I think the intent is right but we can't monkey with the SPA, unless there is some meaningful new clinical piece of data that has emerged one that has been established.

Mr. BURGESS. I thought it was telling, your comment, fail early, avoid the rush, you certainly get why that concept is there.

Dr. Gandy, I really appreciate you being here and appreciate the work you are doing in Alzheimer's. It must have been as startling for you to hear as it was for me that Mr. Carusi is no longer funding Alzheimer's research. But let us talk about that for a minute because one of the first things after I was elected to Congress in 2003, I asked for a meeting with Dr. Zarounian out at the NIH and we talked about things on the horizon, things in the future, and he related that statistic that you gave us, that 5 years delay in the onset of symptoms, big savings on the other side. So if I have done the math calculation correctly where I am now into my third of those 5-year intervals but as you relate, it hasn't really happened, has it?

Dr. GANDY. No, that is right. We currently don't have anything on the horizon that will make an impact on the course of Alzheimer's, on the progress of Alzheimer's disease.

Mr. BURGESS. Well, what about actions like establishing clinical trial networks in the study of Alzheimer's?

Dr. GANDY. The NIA has established a nationwide network of Alzheimer's centers, and that is the mechanism by which it uses to recruit and test new drugs—recruit patients and test new drugs, and that system, that network often partners with industry to test new industry drugs as well.

Mr. BURGESS. And that in turn then spur new investment, perhaps get Mr. Carusi again involved and invested in our research?

Dr. GANDY. I think what we need is a success, and I think that would attract more investors. I mean, we have relationships and

actually a number of public-private fora for discussion but I think the thing that would really build the enthusiasm is some success.

Mr. BURGESS. And would things like standardizing biomarkers, would that help?

Dr. GANDY. That certainly is the—the NIH has established what is called the Alzheimer's disease Neuroimaging Initiative, which has been really a landmark study, ongoing study, in defining a number of biomarkers of the natural aging process, of the conversion from aging to mild cognitive impairment and then conversion from mild cognitive impairment to Alzheimer's disease.

Mr. BURGESS. Thank you.

Dr. Ledley, you brought up a gene therapy, and I can remember reading in the newspapers in the mid-1990s, late 1990s about some promising gene therapies and then unfortunately there were a series of unsuccessful problems, and then it kind of went away. Can you kind of give us an idea of what is on the horizon with gene therapies?

Dr. LEDLEY. So the short answer, gene therapy works. The last couple of years have been incredibly exciting. It has seen some very high-profile IPOs in the past couple years. So people are happy about it again. I think it is a classic story where a lot of—there is a real disconnect between the good support for therapy for NIH, venture capitalists who made a lot of profit early in the field and found a lack of sustained support for the innovations required to take immature technologies and make them mature, and we believe the field has slowed by that. It was a difficult process. There are very important pricing issues for that field to work out in the next couple of years but it is a great example of where the basic science is now ready for investments that can take advantage of discovery and the type of review process which is put in place at the FDA.

Mr. BURGESS. All right. I have more questions, Mr. Chairman, if we have time for a second round, but I will yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Chairman, and both you and the ranking member for asking our witnesses to testify.

First of all, it is frustrating what my mother-in-law went through with Alzheimer's in the 1990s. There is no drug today different from that than Aricept. It wasn't really useful then, slow delay of the illness but we are just not there. And Dr. Gandy, I appreciate all your efforts, and I even appreciate your purple tie, Mr. Carusi, from working with our local Alzheimer's group in Houston.

But let me get to my other issue. The need for greater antibiotic drug development is something I, along with Congressmen Gingrey, Shimkus, DeGette and others, have long championed. We have successfully started getting the ball rolling with GAIN Act last Congress and we are already seeing positive signs. However, as much as it pains me to say, it has not done enough to fully set our country back on a path of investment and development in new antibiotics. We need to combat ever-emerging and deadly diseases. The health of our soldiers and veterans is particularly at risk. An article that ran in The Hill yesterday titled Fighting Superbugs by Developing Targeted Weapons in which the author was Rear Admi-

ral James Kerry stating that many soldiers and civilians have lost their lives because we do not have the drugs we need. It is time to mount an urgent defense against superbugs and use all the tools at our disposal to put new weapons on the field.

Mr. Borisy, I know that knowing that you know about the antibiotic space today, the risk-reward profile, would you advise your clients or colleagues to invest in antibiotic development today, and why or why not?

Mr. BORISY. Investment from a venture perspective in new antibiotic development is very challenging. As an optimist from the science and the medicine perspective, I actually believe we have the tools and the technologies today that if we applied it and focused the capital around it, we could come up with the tremendous innovations that we need against some of these superbugs and areas of very important need to our society in infectious disease.

Mr. GREEN. OK. I only have 5 minutes. But if Congress were to create additional incentives on antibiotic development, do you believe that it might help move the needle with investors such as yourself?

Mr. BORISY. Yes.

Mr. GREEN. If so, what types of reforms or incentives would be needed to improve your outlook on investment in this area?

Mr. BORISY. So one of the most important would be again drawing the analogy from cancer and from rare genetic diseases, which is if we accept it for these antibiotic infections, allowing to develop for those specific populations to show that if we could show that a drug works in those specific populations, that would have a tremendous impact.

Mr. GREEN. I, along with my colleague, Congressman Gingrey, have introduced the ADAPT Act, which is a follow-up on the GAIN law from last Congress. It would create a special designation for critically important antibiotics with a goal of improving FDA process around them. If we could demonstrate to industry leaders such a process would shorten approval times for safe and effective products, would that help increase the worth of antibiotic products on the market?

Mr. BORISY. Yes, it would. It would have a direct impact.

Mr. GREEN. Thank you. Without new antibiotics, medical advances and new cures to treat other diseases will largely be moot since treatments like chemotherapy, even a miracle future therapy could be too dangerous to patients because of the risk of infection and no antibiotics to protect them, and I urge my colleagues to take swift action and aggressive action because we do not have a moment to waste, and again, hopefully our subcommittee will look at the ADAPT Act as a follow-up to the success we are seeing with GAIN. I know just recently there was one of the pharmaceuticals approved.

Mr. Chairman, I will yield back my time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. It is great to be here. I am way down on this side. And it is great—I too am in the other subcommittee so I am bouncing back and forth, but it is really important to hear the plethora of the panel because it really just gets

your mind going. It drives staff crazy because they want us to direct our questions, but you start thinking. So I am going off script for a second.

Mr. Hemphill, Alzheimer's, everyone has been touched by it. So you hear the testimony. Obviously the capital community is not here. There is no return on investment, can't make the case. It is an epidemic. It is going to—so this whole brand exclusivity stuff, I mean, doesn't that not make a case for creating a market condition where capital will flow so they can get a return so we can solve this disease?;

Mr. HEMPHILL. So——

Mr. SHIMKUS. I have got to be quick so——

Mr. HEMPHILL. I am off script.

Mr. SHIMKUS. I am off script too. That is right.

Mr. HEMPHILL. I completely agree that in principle if you have a situation where you otherwise would not have a drug——

Mr. SHIMKUS. Like this, I mean right now, we got it.

Mr. HEMPHILL. Well, I am not sure the case is proved from the fact of long development.

Mr. SHIMKUS. But I will just say, there is no money going right now so the market is making the case now.

Mr. HEMPHILL. The absence of investment doesn't necessarily tell us that a different legal regime would yield a different result.

Mr. SHIMKUS. OK. Let me move forward. That is part of the challenge, this debate that we have to get to.

I also want to just highlight—Mr. Matheson did a great job. I am a cosponsor of the AIM Act for all the reasons that—I am not going to go into it in detail, but I would encourage my colleagues to look at that and get on it.

Mr. Chairman, I would encourage you to—I don't know if we want to wait on this 21st century cures thing or you may want to consider trying to at least get it through the process so we can see where we are because I don't see a downside to it. I just don't. It helps bring capital in the early formation. It is outside the Medicare morass, coding issue. It brings more certainty than less at a time when you are looking for capital flow.

So now I will get on script, Chris. But we are trying to focus in—and a lot of this debate has been on obviously the lifesaving drug that will emerge and the cost, but I think as important in this debate is the diagnostic portion because the way the world is changing and the science behind this, you can target specific drugs to specific conditions based upon markers and the like.

So Mr. Borisy, starting with the premarket approval process, what types of incentives do you believe might spur development in this space? Were you thinking it might be constructed similar to a drug-like postmarket incentive structure or something different?

Mr. BORISY. So for diagnostics, a clear and predictable understanding of reimbursement, which does not exist today, would have a direct connection to capital formation for innovative new diagnostics that we mean and that clear and predictable reimbursement in diagnostics, whether that was in some form of postmarket exclusivity, whether that was just in clear Medicare rules and understanding that clarity and transparency would make a tremendous difference.

Mr. SHIMKUS. In your testimony, you recommend the committee consider a process whereby CMS create a program for diseases important for public health with high unmet diagnostic needs. Can you tell us more about how such a program might work and for instance, could it help cut down the time between FDA approval and the CMS coverage?

Mr. BORISY. So if we take an example that we have been talking about at the hearing today such as Alzheimer's and if we said from the work that Dr. Gandy and others are doing that we had a diagnostic imaging biomarker that we felt was meaningful and predictive, understanding how that would be paid for, just simply having that clarity and stability would allow then the development and proof of that diagnostic. That diagnostic would then enable the development of therapeutics to Alzheimer's that we have been bemoaning here today as lacking.

Mr. SHIMKUS. Yes, and I just want to throw—Mr. Miller is here and in part of his testimony he said on Alzheimer's, it is just the right thing to do. So we have got to change our programs and processes to address this, and hopefully we can get there working together. This is a very exciting time but there are unmet needs that we should be about meeting, and with that, Mr. Chairman, thank you and I yield back my time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentlelady from Florida, Ms. Castor, 5 minutes for questions.

Ms. CASTOR. Thank you, Mr. Chairman. I want to thank the panel for your expert advice today and also commend my colleagues for focusing on this important issue for American families.

We have today about the MODDERN Cures Act, which would extend the period of exclusivity for essentially any new drug to 15 years. That is 3 years longer than any other term of exclusivity currently in the law, and the intent of the bill is very good, but I have been listening closely and I haven't heard today that a case has been made for why there would be a need to extend exclusivity for such a lengthy term, and a number of you have testified to that today and to some of the negative effects of lengthy periods of exclusivity.

Dr. Ledley, could you explain in greater detail how in your view greater exclusivities would discourage uptake by hands of smaller biotech companies?

Dr. LEDLEY. Sure. Fifteen years is a very long time in the progress of science. We don't use 15-year-old computers anymore, and by the time a drug has been on the market for a certain length of time, science is able to come up with something better and should, and the public needs it. So there needs to be a return on the investment in the original drug and there needs to be an immediate turnaround to invest in the next drug that is that much better, and 15 years is just out of proportion to the space of scientific progress.

Ms. CASTOR. And I am also extremely concerned about the price tag for providing extended exclusivities. Dr. Miller, your testimony mentions the Solvadi situation, the hepatitis C drug that is now about $1,000 per pill. It is an extraordinary price but coupled with the fact that we have over 3 million Americans that could have their hepatitis C cured, they would benefit greatly. So that has

raised these difficult questions for public and private payers especially. Could you describe for us the tradeoffs and compromises that payers are having to make as a result, and could you tell us why Solvadi is unique or could it be part of a trend or are there other similarly priced drugs on the market?

Dr. LEDLEY. That is a great point. So what you see is that for manufacturers, they don't have just exclusivity as a lever to pull, they have pricing. So in this country we allow them to freely price, and that is what has happened with Solvadi. If you treat all 3 million patients in the United States, you will spend over $300 billion, which is equal to the entire drug spend for the United States, and when you look at the pipeline, of that 5,400 drugs that are in human testing, there are many that are going to be breakthrough products that also will be at prices that we can't afford. And so it is no good having drugs that people can't afford and so access has to be considered in your policies when you consider extending exclusivity because you are guaranteeing higher prices for longer periods of time.

Ms. CASTOR. And one of the issues that confronts us as the population ages and the call on Medicare will be greater is the fact that we don't allow negotiation of drug prices in America. It is kind of un-American that we don't negotiate by law. This means that drug companies can charge almost any price that they would like, particularly for lifesaving drugs that are the only treatments or cures for a particular disease. In such cases, it is hard to imagine the need for extending the length of time for which they are shielded from price competition by generics.

Professor Hemphill, is America, in having that policy against negotiating drug prices, do we subsidize drug use in other countries?

Ms. CASTOR. Well, certainly, U.S. payers and patients pay a disproportionate part of the research and development that ultimately has a global benefit.

Ms. CASTOR. Well, I thank you for your testimony, and I want to end on the note of even though we might have differences of opinion on the panel on the Cures Act, I think everyone that I heard today was united in the fact that we need to make sure we are committed to basic research, and the fact that the budget battles, sequester, government shutdowns of the past few years has taken a bite out of NIH and sent scientists possibly looking at careers in other countries, is really something that this committee has got to focus on. Dr. Collins said NIH has lost 25 percent of its purchasing power. We are throwing away half of the innovated, talented research proposals. This really should be the committee's primary point, and maybe moving medical research from a discretionary category to something we have a long, sustained commitment.

Thank you, and I will yield back.

Mr. PITTS. The gentlelady's time is expired. The chair recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Mr. GINGREY. Thank you, Mr. Chairman, Ranking Member Pallone, and to the witnesses for testifying today.

You know, the GAIN Act of course was an important first step in addressing a lack of new antibiotic drug development and we have already seen the first successes of the GAIN Act. I am real

happy to have worked with Mr. Green, Ms. DeGette, MR. Shimkus and others on the committee in a bipartisan way to develop the GAIN Act. Obviously—and Mr. Green talked about this a little bit earlier about the ADAPT Act, which of course is follow-on to GAIN and the work that we need to do in regard to that.

I wanted to direct my questions mainly to Mr. Borisy. When making investment recommendations, Mr. Borisy, can you explain how not just potential economic returns but clinical trials and the approval process impact the likelihood that you would recommend to your team investing in a particular drug?

Mr. BORISY. So me and my partners at Third Rock focus fundamentally on early-stage investments in areas of science and medicine where we can make a breakthrough, make a big difference for patients. So if we talk about infectious diseases as an example, coming up with therapies that would work for something where, you know, it is a superbug and nothing works and it is a critical need, that is the type of thing that we would like to do.

When we are considering an area to invest, when we are in the process of translating those out of the basic research that has been done, a lot of work, multiple years before it can even get to the clinic to refine it into being a drug has to be done. This takes tens of millions of dollars. Then we go into the clinical development period of time, and the questions focusing us are two, which is how much money and how long is it going to take until we can get that proof of concept that we have created something that really makes a difference for patients, not the final bar of approval perhaps but that smart people looking at it say that is important, and the second is, does other parts of the ecosystem that we have talked about recognize that as important. That could be public investors so we could take the company as an IPO. It could be a larger pharmaceutical company that is going to take it across the finish line. Things such as ADAPT where we know that the clinical study can be faster, quicker in a specific targeted population that we can really show it works and makes a difference, if that is more doable, then that is what enables our capital formation to invest in that.

Mr. GINGREY. Well, cutting right to the chase, let me ask you this follow-on. And I think Mr. Green asked you this question but maybe I would like for you to elaborate a little bit more.

Knowing what you know about the antibiotic space today, the risk-reward profile, would you advise your clients or colleagues to invest in antibiotic development today, and why or why not?

Mr. BORISY. And this is not an academic question to us. Actually yesterday morning before flying down here to Washington, D.C., I was looking at an innovative technology in infectious diseases that could do exactly what we all here talking about want it to do, and it is a very difficult question for us right now because it is that question of regulatory uncertainty in the area, and so it is something that we want to be able to do but as we have talked about, the question of if we can do what we have done in areas of cancer and rare genetic diseases with breakthrough therapies, accelerated approvals, it could make it very doable.

Mr. GINGREY. And the last question in my remaining minute, again, Mr. Borisy, my colleague Gene Green and I introduced, as you know, the ADAPT Act, which 23 other members of this com-

mittee have cosponsored. The legislation allows the FDA to approve antibiotics that treat serious and life-threatening infections for specific patients based on smaller and then more rapid clinical trials. Do you believe if Congress could streamline the approval process for such products without lowering the FDA's safety and effectiveness standards the climate for investing in new antibiotics wou8ld improve?

Mr. BORISY. Yes, it would.

Mr. GINGREY. Well, I thank you very much, and I don't have time to address the other members of the panel—it is a large panel—but again, I am grateful that you all are here.

Without new antibiotics, advancements in new cures to treat other diseases would largely be moot since treatments like chemotherapy, even a miracle future treatment, would be too dangerous to patients if you didn't have these antibiotics because you wipe out the bone marrow, you lower their resistance to infection, and as you well know, in many cases the patient doesn't get the cure because they get wiped out and get overwhelmed with an infection and die before the bone marrow has a chance to recover. So all of this is interrelated very closely.

Thank you very much, Mr. Chairman. I yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentlelady from Virgin Islands, Dr. Christensen, 5 minutes for questions.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman, and I thank the panelists for being here this morning.

I am going to direct my questions to Mr. Hemphill. Your testimony describes various types of market protections that are granted to brand drugs in current law and you assert that those protections are, for the most part, functioning quite well. So I am correct in interpreting that in your testimony, that they are functioning quite well?

Mr. HEMPHILL. So my testimony is that they have been effective in providing strong incentive for drug makers to innovate.

Mrs. CHRISTENSEN. OK. Obviously there are many diseases for which no effective treatments exist. You mentioned the possibility that some drugs are not developed because pharmaceutical companies do not view current protections are providing an adequate reward but you state that the scope of the problem is unclear, and I would assume it is also unclear whether weak market protections, if they exist, are actually the cause of failures by companies to develop new treatments. Can you say more about the impact of so-called weak market protections?

Mr. HEMPHILL. Sure. So two brief points on this. One, I think we just don't know a lot about the innovation that doesn't happen. We have anecdotes but we don't have hard data so the data collection effort that was mentioned earlier seems really important.

Second, even though limited protection, the limited non-patent protection that is provided, for example, by the Hatch-Waxman Act, has a big effect. We have therapies on the market that have no patent protection. An Alzheimer's drug, if it a great Alzheimer's drug, suppose they only get 5 years of new chemical entity protection but 20 million people are taking it, and each are a $1,000-a-year business for the brand, not an unreasonable amount judged from what

other chronic diseases have as a pay. A thousand times 20 million people, 10 million people times 5 years, and that is a $50 billion business which I think would focus the mind if you have the kind of excellent drug that we are talking about. Now, that is not going to answer every question but I think for some drugs, a lot of times the existing protections are going to be adequate.

Mrs. CHRISTENSEN. Are there other factors that might be causing delays in the emergence of new lifesaving treatments that we haven't discussed?

Mr. HEMPHILL. Well, sure. I mean, we have talked a bit about just the nature of scientific inquiry and the uncertainties in solving really tough problems like Alzheimer's and cancer.

Mrs. CHRISTENSEN. It is clear we have a lot to learn about how much a problem this even is but we are hearing a lot of conclusions from some of our witnesses today about insufficient patent protections being the cause of pharmaceutical development failures. Mr. Hemphill, have you heard anything in the other testimony today that convinces you that others on this panel have new facts and new data to substantiate this problem?

Mr. HEMPHILL. So I think we certainly have new anecdotes, and it is quite possible that in principle that as we get better at science, the remaining problems are harder and therefore require new solutions. I think the question is nailing down what that other world would look like were we to engage in the kind of changes that are being proposed.

Mrs. CHRISTENSEN. And finally, we have heard a lot today about the need for new incentives. A major focus has been on marketing protections like exclusivity and patent extensions. Mr. Hemphill, your testimony briefly described some other incentives that you indicate could be affected such as providing government funding for certain research and development itself. Can you maybe give us some more ideas about what other incentives are out there and whether you think they hold potential to spur innovation?

Mr. HEMPHILL. Sure. Just briefly, we hear about extremely lengthy trials sometimes being a problem vis-a-vis patent protection because if the patent runs out before you can get your drug to market because of the long trial, the Hatch-Waxman renewal or extension of patents might not be enough. But in those situations where we feel some confidence that this is a worthwhile project to pursue, you could readily imagine, it is a subsidy, it is a government outlay to support those trials. We see this sometimes in cancer, and I think that has been effective, and that is the kind of targeted solution that I think we should really be paying a lot of attention to.

Mrs. CHRISTENSEN. Thank you. Thank you, Mr. Chairman. I yield back.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman.

I am the Republican chair of the Rare Disease Caucus, and in that capacity, I frequently meet with patients and families where there are no medicines, and I am the sponsor of MODDERN Cures. MODDERN Cures is completely bipartisan in its sponsorship, and

I want to thank all of my colleagues who have become cosponsors including, for example, Mrs. Eshoo, Mr. Butterfield, Mr. Tonko, distinguished members of this committee on the Democratic side, as well as Republican cosponsors I see, Mrs. Ellmers and Mr. Bilirakis right in front of me.

Mr. Boutin, can you give your perspective on the incentives in the Orphan Drug Act, which is an improvement in orphan-drug therapies from the original Hatch-Waxman Act, a monumental piece of legislation, whether regarding the Orphan Drug Act and whether you think it is sufficient to incentive rare-disease research or should we be doing more?

Mr. BOUTIN. Thank you for the opportunity.

Mr. LANCE. Certainly.

Mr. BOUTIN. Orphan Drug Act is a monumental piece of legislation. I think everybody in the room recognizes that. But at the same time, we have approximately 8,000 rare diseases.

Mr. LANCE. Yes.

Mr. BOUTIN. We have 500 treatments.

Mr. LANCE. Yes.

Mr. BOUTIN. Clearly, we need to do more.

Mr. LANCE. Yes. And regarding Alzheimer's and the moving questioning of my colleague, Congressman Green, would it be fair and is this the consensus of the panel that we need to do a much better job regarding Alzheimer's and somehow have to reach a solution to bring that to a better situation for the hundreds of thousands, indeed millions of patients who will suffer from Alzheimer's? Is that the consensus of the panel?

Mr. BOUTIN. Without question.

Mr. LANCE. Is there anyone who dissents from that? Thank you.

Professor Hemphill, in responding to Congressman Shimkus's questioning, I believe you said—and I am paraphrasing and I certainly want to give you the opportunity to respond fully—I believe you said that the absence of new drug therapy doesn't necessarily mean that we need a new legal regime. Is that what you said? And I certainly want to give you every opportunity to express your point.

Mr. HEMPHILL. Yes.

Mr. LANCE. You did say that?

Mr. HEMPHILL. Yes. Do you want me to explain?

Mr. LANCE. Of course.

Mr. HEMPHILL. So the idea here is simply that we don't know simply by the fact of increased legal protection that we will thereby have new cures.

Mr. LANCE. Yes, I am an attorney, and we do not know. It seems to me we need some progress in these terrible rare diseases and not so rare diseases like Alzheimer's, and of course, we cannot be conclusive that a new legal regime would bring that about. Is it possible that modification of the current legal regime would bring that about?

Mr. HEMPHILL. As I said, in principle, it is possible. What is tricky here is that we know a lot about the costs from length and exclusivity vis-a-vis drugs that are going to be elicited either way and we know almost nothing about the theoretical improvement that we would get from a longer period of——

Mr. LANCE. That is why we need a healthy discussion to reach a balance.

Mr. HEMPHILL. Agreed about a balance.

Mr. LANCE. And at the moment, there is the balance in Hatch-Waxman and then there is the balance in the Orphan Drug Act and we are trying to move forward in rare diseases, I, as the Republican chair of the Rare Disease Caucus. We need a healthy balance, and that is what this committee in particular is trying to strike, and I would encourage all on the panel to determine what that healthy balance should be, and Mr. Boutin, you believe we need to update or at least modify orphan drugs regarding rare diseases?

Mr. BOUTIN. Without question, we need to update the balance, strike it better, and two quick points. The anti-evergreening issue that was raised applies to every medication——

Mr. LANCE. That is precisely accurate.

Mr. BOUTIN [continuing]. Not what would be on MODDERN Cures. The issue around costing currently applies to every medication, not what would come out of MODDERN, just to be very clear.

Mr. LANCE. Thank you.

And finally, Professor Hemphill, I don't think we have ever met before. You are welcome to come into my office at any time to discuss my legislation, MODDERN Cures. I understand you teach in Upper Manhattan and live in Manhattan, and I assure you, the Lincoln Tunnel, the Holland Tunnel and even the George Washington Bridge are all open, and I welcome healthy discussion on my completely bipartisan legislation, MODDERN Cures Act.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from New York, Mr. Engel, 5 minutes for questions.

Mr. ENGEL. Well, thank you very much, Mr. Chairman. I live on the other side of the George Washington Bridge, the side that people couldn't get to when it was blocked, so I want to thank all of you for your testimony and especially give a call out to the New Yorkers, Dr. Gandy and Mr. Hemphill. Always good to see New Yorkers down here in Washington.

The 21st Century Cures Initiative creates an important bipartisan opportunity for us to consider creative new approaches to incentivize getting new treatments into the hands of patients as quickly and safely as possible. I am the coauthor of the Paul Wellstone Muscular Dystrophy Community Assistance Research and Education Amendments of 2008 and 2013 along with my colleague on this committee, Dr. Burgess. I have seen how new research models have produced great advances in our understanding of the various forms of muscular dystrophies. So I raise this now because I think we can use the Wellstone Muscular Dystrophy Research Centers' model to incentivize other forms of research. Much like the National Pediatric Research Network, the Wellstone Centers use a network approach that is designed to ensure that research is not conducted in silos, and I believe this network approach fosters collaboration and allows government funding to be supplemented by nonprofits and patient advocacy dollars and by private biotech and pharmaceutical funding.

Let me ask you, Dr. Gandy, given your experience with Alzheimer's research at Mount Sinai, could you comment on how a network approach to research can serve as a force multiplier to incentivize treatments and cures for patients?

Dr. GANDY. I think the network approach is essential. For one thing, the network standardizes the approach to medication, the approach to diagnosis across all centers, and by disbursing the person power across the country enables the rapid recruitment of new subjects for trials. I think in terms of operations, there is really no other way to do it.

Mr. ENGEL. Are there any other models of public-private partnerships that you think would be constructive to consider in addition to the Wellstone Center approach?

Dr. GANDY. No, I think that is a reasonable place to start.

Mr. ENGEL. OK. Thank you.

I would also like to ask about the development of treatment and cures for patients with rare diseases. Within our rare-disease research communities, more and more personalized approaches to therapeutic development are becoming possible but these lifesaving personalized drug therapies have small consumer markets and are among the most expensive therapeutics ever created. So let me ask Mr. Borisy and Dr. Miller, could you comment on how we can continue to attract biotech and pharmaceutical industry partners into this space and how we can support industries' work with payer groups to ensure access once therapies are approved?

Mr. BORISY. So on the investing in new potential companies that are focused on rare genetic disease, if we believe the science and medicine is there to really make a tremendous different for the lives of those patients, my partners and I are one by one working through those opportunities and forming multiple companies to do exactly that. Part of that is based on the understanding as we have talked about here today on the path through regulatory approval. A second part is understanding the reimbursement as being there, and when we are talking about diseases that might have a couple thousand patients, a couple hundred, or some that are even as few as 100 patients that are involved, that necessarily means a high price associated with those, and we know those are challenging issues. There are potential therapies that could make a huge difference for patients. If we have stable reimbursement, even at those high prices, then innovation in those rare diseases will continue.

Mr. ENGEL. Thank you.

Dr. Miller?

Dr. MILLER. Yes. What has been proven that makes a difference for these diseases is, one, NIH funding, so having basic science to support it. So even when we look at Alzheimer's, it is rarely about the basic science that is going to drive the industry development. Second, it is actually the FDA. You have heard from everyone, it's regulatory and reimbursement certainty. That is actually their bigger risk than looking for added incentives, and so if you are really going to concentrate on the things that help everything from antibiotics to Alzheimer's to rare diseases, it is really about regulatory and reimbursement certainly.

Mr. ENGEL. Thank you. I see my time is up.

I was wondering if I could just ask one more. Many of you have mentioned that funding basic science through funding the NIH is critical to the goal of creating incentives for innovation, and I certainly agree.

So let me ask Dr. Miller and Dr. Ledley, if either of you could tell us more about how basic science gets translated into cures that can then be capitalized upon by drug makers and what effect have recent cuts to NIH's budget had on this process?

Dr. MILLER. So I started as an NIH investigator. My wife is the Chairman of Medicine at Washington University. The NIH budget cuts have been devastating to basic science research at universities. The great thing about the NIH is they allow the investigators to actually spin these products off and work with the venture capitalists to start new companies. When you stop that process, when you choke off at NIH the basic science level, the rest of the process doesn't work and so it is crucial that we restore and even improve funding for basic science.

Dr. LEDLEY. I think we have heard big numbers about how many rare diseases and how many unmet needs there are, and there are enormous numbers. I think it is useful to look at the number of grants the NIH puts out every year relative to that number and ask how many investigators do we think should be taking independent new initiatives for these diseases, each one of which harbors the potential for the new cure that can then be developed.

Mr. ENGEL. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Louisiana, Dr. Cassidy, 5 minutes.

Mr. CASSIDY. Thank you, Mr. Chair. I really enjoy the panel.

Now, Mr. Hemphill, I have to say when I read your testimony, your spoken testimony had something different. I say this not to challenge, merely to understand. You said listen, you don't think extending exclusivity is necessarily important but when you spoke you said except maybe as Dr. Gandy suggested. Now, clearly you left a door open there. Do you see that there is circumstances in which this extension of patent protection exclusivity for something particularly like I think you used the example of an oral therapy for neuromuscular disease or neurologic disease would indeed be helpful?

Mr. HEMPHILL. So I certainly didn't intend any inconsistency between my written testimony and my oral. I feel strongly that if we have clear evidence that a targeted increase in exclusivity would work, we should take that really seriously.

Mr. CASSIDY. Now, hang on, and again, this is a great conversation, so I am not saying this to challenge but there is a certain existentialism about this, right?

Mr. HEMPHILL. Right.

Mr. CASSIDY. Now, we cannot know the future, and so we are always going to have the anxiety that oh, my gosh, I made the wrong decision.

Mr. HEMPHILL. Right.

Mr. CASSIDY. I do that whenever I buy a stock. So that said, we know Gandy. He is an incredible investigator, which by the way, the NIH 20 years ago was advised to redirect their funding to things which have more importance to modern disease. They have

not done it in 20 years. So as we speak of the NIH, let us note that the IOM has suggested that they redirect funding and they have not done so, and in a period of constrained resources, we have to call upon them perhaps to be a little bit more directing towards your diseases.

Now, that said, I go back to my point. Is there a kind of situation in which indeed these sorts of incentives would be important?

Mr. HEMPHILL. Yes. Certainly that is possible, and I also don't mean to suggest that certainty has to be our standard. As you say, we are investing, we are gambling, but we are gambling with the public's money to the extent that——

Mr. CASSIDY. I agree.

Mr. HEMPHILL [continuing]. Existing drugs get this extension, which is why I say narrowing our view not to every single drug and probably not every single——

Mr. CASSIDY. So let me challenge you. Are you ready, man?

Mr. HEMPHILL. Yes.

Mr. CASSIDY. You are a bright guy. Figure out that metric and give it to Lance. That would have an incredibly important—because I look at Alzheimer's, and there is few models I think outside of Down's kids of where you know they are going to develop disease.

Now, as the son of a man who died of Alzheimer's, this is so incredibly important. If you could figure out that metric talking to Gandy across town, that would be fantastic for our country. So I say that just to kind of put the plug in.

Mr. HEMPHILL. I appreciate that.

Mr. CASSIDY. Yes, thanks.

Dr. Miller, good to see you, man. Listen, I have some problems with your California study. I am a hepatologist. And so if you look at the intention to treat, I do think they underestimate the impact of Solvadi upon outcomes. Every time I still see patients mentally ill and such who are not candidates for interferon, wouldn't be included in a clinical trial so the 47 percent cure rate that that paper posits, it doesn't happen among my patients with addiction disorders or mental illness. That said, I am struck that you suggest that we need to have a mechanism by which we would limit what a company could charge but you don't mention that mechanism. And I say that because your company is incredibly disruptive. I mean, you all are good. So you think about how markets work. Do you have a suggestion how the Federal Government could limit what companies charge without squelching the innovative drive that has given us a drug which is truly a breakthrough drug?

Dr. MILLER. If you interpret what I said as the government should be price-setting, the answer is absolutely not. We do not believe the government——

Mr. CASSIDY. And you didn't say that but I didn't know where you would go with it.

Dr. MILLER. No, we actually believe it is a free market solution that has to be required, and so we look at it the exact opposite. We think that they have taken advantage of it, which is just a warning to you all that when you talk about extending the period of exclusivity, remember that that is not the only lever that these people have. They have pricing as a lever and they clearly have exercised it, and Solvadi is a great example of it, but we believe that the

pushback to Solvadi has to come from the marketplace, not from the government.

Mr. CASSIDY. So if we are talking about patent protection, it seems like there is limited levers to push back form the marketplace. Is that a fair statement?

Dr. MILLER. So you know——

Mr. CASSIDY. And again, we are kind of guessing what their true cost is to develop a drug, which is an incredible drug.

Dr. MILLER. So we actually know in this particular case their true cost of developing it because they didn't develop it, they bought it for $11 billion and they will make that back in the first year alone. The trouble is, is that you also need the pharmaceutical manufacturers to act responsibly in their pricing, but even in that absence, there is going to be competitors to the marketplace and they will have to pay a consequence if the competitors can create a product that is equally good because, as you said, we will shift our market share to someone that is willing to give us a better price.

Mr. CASSIDY. Well, I am out of time. I really enjoyed the written testimony and I wish I had more time to ask questions, and thank you each for your good work. I mean, I thank you each for your good work. Thank you.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentlelady from North Carolina, Ms. Ellmers, 5 minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you to our panel for being here today.

You know, the 21st Century Cures is certainly something that I have considerable passion for, and I think it is certainly the right approach for us to take in government when unfortunately, many times we are always reactive rather than proactive.

My first question is for Mr. Borisy. We have all discussed the challenges of costly cures to come up with for diseases. Again, Alzheimer's is a devastating disease. Certainly I know many of us have been touched by this personally. My mother died of Alzheimer's, and we all want a cure, and I hear this from my constituents all the time, "I don't understand, you spend so much money in Washington on so many different things, why can't you come up with a cure for Alzheimer's, why can't you come up with a cure for diabetes." We know how much this affects the American people.

I think I have a better understanding from listening to the testimony that you are all giving today, that the cost and the benefit are not necessarily adding up, and that forces some of the innovations, research, and the development outside of our own country. What can we do here in Washington, right now, as part of this 21st Century Cure, what changes in policy can we make and what specifically—I know a lot of it is the length of time—it is the FDA. If you had one thing that you could say would change this dramatically, what would it be?

Mr. BORISY. So we want to bring these innovations to patients, as you just very eloquently said. Of course, the science and the medicine, the basic science and medicine has to be there, but with it there, what we can do is if we can apply the tools that we have learned from accelerated approval, from breakthrough therapies

with FDA to say as a society that we want to apply those for these chronic diseases like diabetes, like Alzheimer's, that simple act alone will change the consideration of the game. It doesn't guarantee we will successfully create——

Mrs. ELLMERS. Right. No guarantees. That is never——

Mr. BORISY. But it totally would change the game that if there are ideas and sparks out there, it makes it something that is investable in to go take that risk.

Mrs. ELLMERS. So again, it is getting back to uncertainty that is out there and the unfortunately—we are talking about dollars. I mean, we are talking about investment. We are talking about folks putting their hard-earned money behind these initiatives, and there has to be a payoff, and you know, sometimes that is hard for us because again, we are passionate about the issues and it is a very emotional and personal issue.

Mr. Carusi, one of the things—again, it gets back to the availability to be developing drugs. I have a business company in my district, Entera Health, which is a medical foods company. Basically, this is one of the innovations that we are seeing moving forward. For patients, medical foods, and helping patients who are taking many of these medications for HIV, Parkinson's, Alzheimer's, rheumatoid arthritis, irritable bowel syndrome, and helping the patient to respond better to drugs. How can we help this process when we are talking about reimbursement? How can we do a better job to make sure that there again we are making this advancement? What changes at the FDA level would you say would streamline this process for something that is on the edge as we are talking about medical foods?

Mr. CARUSI. Yes. Medical foods is not an area where I have been heavily focused or invested, but again, I think the theme that you have heard is one of consistency, transparency and predictability, and when you start to have, as you defined it, devices, drugs, therapeutics that are on the fringe, the pathways start to become less defined, less certain, and so as a result, any of these approaches, we need to know with clarity starting with FDA what the path is and then with reimbursement if these were indeed reimbursed products what that looks like, what the bar is and will they be reimbursed. Alternatively, some of these may be self-pay opportunities and that has its own set of discussions. But all of these testimonies and all these discussions, it comes back to transparency, certainty, and predictability.

Mrs. ELLMERS. Thank you. I have just one quick question. Does CMS now have the authority to create codes? Because I know this is a conversation we have had in the past where we have reached that level and then we have to unfortunately see another level realized. Do they have that authority right now?

Mr. CARUSI. To create codes?

Mrs. ELLMERS. To create codes.

Mr. CARUSI. My understanding is—around medical foods specifically or more——

Mrs. ELLMERS. Well, not necessarily around medical foods.

Mr. CARUSI. My understanding is yes, but again, this is starting to get to the—there are others that are more knowledgeable in that area than me.

Ms. ELLMERS. Thank you, Mr. Carusi, and I have overstepped my time, so thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Dr. Gandy and Mr. Borisy and also Mr. Carusi, let us talk about increasing incentives. I know that it was mentioned earlier. We want companies to continue to invest in new and innovative treatments, but it seems to me there are so many diseases that currently go without treatment options. In your testimony, you all touched on extending exclusivity and patent life. Can you elaborate on how market exclusivity, data exclusivity and patent life play a part in driving innovation for treating neurological diseases such as Alzheimer's or perhaps Parkinson's, and how if we do nothing this could hurt the development of new innovative therapies? Why don't we start with Dr. Gandy?

Dr. GANDY. I would say in my experience over the past 30 years, I have watched the pharma and VC investment in Alzheimer's research dwindle and the single reason that is most frequently cited is the regulatory path, the challenge for getting approval and then having sufficient patent life left to recoup any of the investment. Alzheimer's disease moves very slowly. The clinical trials require hundreds of patients. They take years to complete, and it is a monumental task, and we don't have yet any templates. We are trying to do something in biology we have never done before.

Mr. BILIRAKIS. Thank you. Mr. Borisy, please.

Mr. BORISY. Two weeks or so ago, I was talking with a senior pharmaceutical executive who is running a program in Alzheimer's, literally spending billions of dollars over many years. If we are to try to create and invest in a company that is going to pursue Alzheimer's therapeutics, given that type of scale of time and money that is required, we need to have confidence that if we get to some early stage of proof of concept in the clinic that a future partner, be that a pharmaceutical company or be that public market investors, will believe or be willing to take on the risk from there, we need to be able to hand the ball off to the next stage in the ecosystem for it to have been a viable place to put our money in the beginning. If for the next step in the ecosystem they literally are spending billions of dollars and an indefinite period of time, then they will say you have created that innovation but there is no protection left for that product and therefore even if we show that proof of concept, they will say but that has no value to us. That is a fundamental impediment to us investing in companies in the area.

Mr. BILIRAKIS. Thank you. Mr. Carusi, please.

Mr. CARUSI. Yes, I think it comes back to time, and so I want to give an example. In my portfolio of companies, we have a company GI Dynamics, and GI Dynamics is developing a device-based approach to treat type 2 diabetes and obesity, two of the biggest chronic-disease issues we have in this country. We first started that company in 2004. It is now 2014. We are still in the midst of running our clinical trial for FDA approval and we are starting to commercialize the product outside of the United States. If you had asked me today, oK, you know, 10 years back, would you invest in this company knowing you weren't going to have approval until

2015, 2016, I wouldn't have made the investment despite the fact that what they are doing is tremendously valuable. So it comes back to the incentives and whether or not if it is going to take this much time and this much money that again we can make a reasonable return on that investment, and to me, it is a math problem and that is what this comes down to, and I do think there are certain areas, and I think they are in the chronic-disease field, where there are big studies a lot of times huge potential but we are going to need help, and I think that is what we are asking for.

Mr. BILIRAKIS. Very good. Thank you.

Can anybody on the panel give me a rundown on Parkinson's disease, if there are any promising therapies, breakthroughs, maybe delaying the onset of Parkinson's disease? Is there anybody on the panel that would like to discuss that?

Dr. GANDY. The Parkinson's disease field is now following in the template of the Alzheimer's field in terms of generating these networks that are nationwide looking for biomarkers. I think that they have the advantage of having a little more in terms of impact using transmitter replacement and manipulation than has happened with Alzheimer's, so there are some new medications there targeting some new receptors for symptomatic relief, but they haven't yet changed the progression of the disease, and that is really what the key is, to slow the progression.

Mr. BILIRAKIS. Anyone else?

Dr. LEDLEY. A lot of good work on gene therapy. This came up earlier, but this is one that is a challenging target but clearly a feasible and difficult one, but a lot of good work. Some of the companies that have raised money lately are doing it aimed at Parkinson's.

Mr. BILIRAKIS. Very good. Thank you.

Thank you, Mr. Chairman. I appreciate it. I yield back.

Mr. PITTS. The chair thanks the gentleman. I hate to cut this off, but this has been the best interaction we have had with members and witnesses, and frankly, this has been one of the most informative, helpful, exciting hearings that we have had. So I want to thank each of the witnesses for your testimony. We have a UC request?

Mr. PALLONE. Thank you, Mr. Chairman.

Let me echo what you said about the hearing and the value of it. I totally agree.

I just would ask unanimous consent to enter into the record the statement of Ann Boynton, Deputy Executive Officer for the California Public Employees Retirement System.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. Without objection, so ordered.

There will be follow-up questions. We have members at other hearings on the floor. Dr. Burgess is having to manage time on the floor. We have follow-up questions. We will submit those to you in writing. We ask that you please respond promptly. I remind members that they should submit their questions by the close of business on Wednesday, June 25th.

Again, thank you so much, a very good hearing. Without objection, the subcommittee is adjourned.

[Whereupon, at 12:38 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREMIER TRANSFORMING HEALTHCARE TOGETHER

Statement for the Record

Submitted by

The Premier healthcare alliance

House Energy and Commerce Subcommittee on Health

21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients

June 11, 2014

The Premier healthcare alliance appreciates the opportunity to provide a statement for the record of the House Energy and Commerce hearing, titled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients." Premier, Inc. is a leading healthcare improvement company, uniting an alliance of approximately 3,000 U.S. hospitals and 110,000 other providers of care to transform healthcare.

Together, Premier's hospitals, post-acute care sites and other providers are seeking better ways to reduce the fragmentation of healthcare and increase coordination of care. Premier operates a number of large-scale collaboratives, including those focused on bundled payment and accountable care organizations (ACOs), in which Premier health systems push for improved quality at a reduced cost.

We applaud the leadership of Chairman Rep. Joe Pitts and Ranking Member Frank Pallone, Jr. for holding this important hearing. While there are many initiatives our alliance members can undertake on their own to improve the quality, safety and affordability of healthcare, continued government action is needed to fix perverse payment incentives and foster greater collaboration and innovation in the U.S. healthcare system.

The Medicare program, which sets overarching incentives in healthcare as the main payer in the marketplace, is a vital resource for beneficiaries and providers. However, the current system creates fragmentation and competition among healthcare providers which discourages cost-effective innovation.

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This is largely due to the fact that Medicare pays in silos. Different types of providers—hospitals, physicians and post-acute care providers—are all paid separately, putting providers in competition, rather than cooperation with one another. This creates a micromanaged system with competing interests that can directly lead to waste, inefficiency and patient frustration. Moreover, the system is overburdened with laws and regulations that prevent collaboration among healthcare providers, and it stands in the way of innovative efforts that could improve the quality, cost effectiveness and coordination of care for Medicare beneficiaries.

To break down the silos of care and unlock innovation in healthcare, new value-based models, such as ACOs and bundled payments are being implemented. These models encourage collaboration among healthcare providers, innovation and a focus on the patient. Representing a positive shift in healthcare delivery, these new approaches promote what health care needs: aligned incentives that will lead to collaboration among physicians, hospitals, payers, and patients.

Aligning incentives across the continuum of care through bundled payments

Premier believes that a particularly promising approach that breaks down the existing silos of care, aligns providers' incentives and encourages greater coordination is bundled payment. Because of the goal of coordinating care, bundled payments can include participation by multiple provider types across the continuum of care.

The concept of bundled payments is not new, and has in fact already been tested by the Centers for Medicare & Medicaid Services (CMS) through the Acute Care Episode Demonstration, among other programs, and such arrangements are successfully operating in the private sector. Premier members have participated in these programs, as well as the Center for Medicare & Medicaid Innovation's Bundled Payments for Care Improvement (BPCI) initiative that is currently underway. This model allows providers to bid as a team for fixed price reimbursement for physician payment, nursing-home care, surgery and medications, primarily for common treatments such as heart surgery or hip and knee replacements. Paying for care in its entirety, rather than having providers bill insurance companies separately, has advantages that directly benefit patients. Paying a fixed price incents providers to collaborate to ensure the best outcomes.

Paying for an episode of care has also been shown to lower costs–both for providers and patients. A Medicare heart bypass surgery bundled payment demonstration saved $42.3 million, or roughly 10 percent of expected costs, and reduced patient insurance costs by $7.9 million while improving care and lowering mortality rates.

At the same time, it is important that there be safeguards in an ACO or bundled payment system to protect against stinting on care. These include robust quality measures and a limitation on provider risk for high-cost patients or the introduction of proven, high-cost new products and technologies.

However, we believe it is time to move beyond these pilot programs and implement a broad-scale, voluntary bundled payment program that is available to providers nationwide on a permanent basis.

With the investment of time and resources needed to implement bundled payments, providers can be reluctant to engage in these transformative efforts because of uncertainty about whether such payment systems will ever be deployed widely. The enactment of a national, voluntary bundled payment program would provide certainty to providers by placing a stake in the ground, signaling that Congress and CMS are dedicated to improving quality and safely reducing costs for Medicare beneficiaries through such a mechanism. This will assure providers that bundled payment is not a passing fad, but one they can invest in for the long term.

With sustained diligence and oversight by Congress to advance models such as bundled payments that give providers the flexibility to innovate and create incentives for efficiency and better care coordination, we are confident that we will continue on the path toward higher quality care while bending the cost curve.

GPhA
Generic Pharmaceutical Association

Statement for the Record

Energy and Commerce Subcommittee on Health

U.S. House of Representatives

Hearing on "Examining the Role of Incentives in Advancing Treatments and Cures for Patients"

June 11, 2014

Submitted by the Generic Pharmaceutical Association

The Generic Pharmaceutical Association (GPhA) appreciates the opportunity to submit this statement for the record. GPhA represents the manufacturers and distributors of finished generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals, and suppliers of other goods and services to the generic industry.

The United States is fortunate to have the most competitive and innovative prescription drug market in the world. The pharmaceutical industry can trace much of its current success back thirty years to the passage of the Hatch-Waxman Act. With this law, Congress created a precise balance between access to lower cost generic medicines and incentives to innovate new and better medicines. This balance has now been in place for three decades and has delivered public health and economic benefits far greater than could have ever been imagined when President Reagan signed the bill into law. As a result of Hatch-Waxman, the U.S. is now home to the world's most robust generic market with the highest rate of generic utilization, has the largest brand drug market, and the highest amount of pharmaceutical research and development spending.

Access to Affordable Medicines

Prior to the passage of Hatch-Waxman, patients had very limited access to generic alternatives. In the first year after Hatch-Waxman, however, FDA received 1,050 ANDAs (generic drug applications). By the end of the second year, generic drugs accounted for about 22 percent of all prescriptions. By 1990, generic substitution had reached 30 percent, and annual savings were approximately $5 billion. By the end of first decade, generic substitution had reached 42 percent and annual savings were $30 billion. After 20 years of Hatch-Waxman, generics were accounting for half of all prescriptions dispensed in the United States, and annual savings generated by generic drugs use reached $69 billion. Today, generics account for 84% of all prescriptions in the United States, and annual savings have reached $217 billion.[1]

[1] Annual generic utilization and savings data compiled from IMS Health, the Generic Pharmaceutical Association, and the Congressional Budget Office.

The use of lower cost, FDA-approved generics will continue to be critical to the sustainability of our healthcare system in the coming decade. IMS Health estimates that as access to healthcare expands and the demand for medicines increases, annual spending for prescription drugs will rise to between $420 billion and $460 billion by 2017, up from the current annual spending level of about $330 billion.[2] Without the savings generated by the use of generic medicines, which on average cost up to 70 percent less than their brand name counterparts, drug spending in 2017 (assuming the same level of drug use) would exceed $1 trillion.

Competition Drives Innovation

The enactment of Hatch-Waxman and the resulting introduction of robust generic competition has been a catalyst for investments in research and development by brand pharmaceutical manufacturers. The competition in the pharmaceutical marketplace currently provided by generic drugs – and the competition that biosimilars will soon provide – is vital in both assuring patient access to life-saving cures and in spurring innovation and research into new cures. The Congressional Budget Office (CBO) has noted that since the law's enactment in 1984, private sector spending on research and development increased from $8 billion to $50 billion in 2008, with annual increases of approximately 9% per year.[3] PhRMA reports that, "In the last ten years, more than 300 new medicines have been approved by the FDA, helping patients live longer, healthier lives."[4] The 2009 Medco Drug Trend Report reported that "about one-third to one-half of the products in Phase III development are new molecular entities (NMEs), new therapeutic biologics, or new vaccines/blood products; the remainder involve new indications for existing drugs, new combination products, new dosage forms, or new routes of administration."[5]

Another example of competition driving innovation is the Biologics Price Competition and Innovation Act (BPCIA), which the President signed into law in 2010. Currently, the FDA is implementing the BPCIA, which establishes the new pathway for generic versions of biologic drugs, known as biosimilars. The intent of the BPCIA is to bring competition to the biologics market in the same way that Hatch-Waxman brought competition to the small molecule drug market. Biologics are the future of medicine and are often the only lifesaving treatments for the most severe diseases, but their high price tag can keep them out of reach for many patients. Capturing the opportunity to make lifesaving biologic medicines available to millions of patients at lower cost is a priority objective for our industry, and generic manufacturers are working actively in this field.

Looking Ahead

GPhA has member companies that manufacture both brand and generic products, so we

[2] IMS Institute for Healthcare Informatics. "The Global Use of Medicines: Outlook through 2017," p. 13. (November 2013)
[3] Congressional Budget Office, Economic and Budget Issue Brief. "Pharmaceutical R&D and the Evolving Market for Prescription Drugs." (October 26, 2009)
[4] Pharmaceutical Research and Manufacturers of America. "Explore the Latest Progress on Medicines in Development." (2014)
[5] Medco. "Drug Trend Report." (2009)

understand the importance of a balanced approach that fosters both innovation and competition. When looking at economic and other types of incentives to spur drug development, it is important to take a holistic approach and focus on the specific reasons why companies are not investing in certain drug treatment areas. Is it because the cost to conduct clinical trials continues to grow? Are there regulatory barriers? Are there reimbursement issues? Is additional federal funding for basic research needed? Pinpointing the reasons for lack of investment can help identify the appropriate incentive.

Legislative proposals intended to incentivize investment in biomedical research and the development of new drugs should avoid unnecessary intellectual property or exclusivity incentives that could act as barriers to generic competition, which has proven to be a driver of new drug innovation, and thereby create an incentive for inefficient and non-innovative research and development. The goal should be for companies to direct funding to the innovative discovery of new cures rather than rewarding the development of non-innovative, "me too" products. As Dr. Fred Ledley of Bentley University noted in his testimony for this hearing, "Extended exclusivity for existing drugs or biologics can create incentives for incremental innovation, making companies less likely to discover and develop new medicines; less likely to enter into alliances with entrepreneurial biotechnology companies; and less likely to make acquisitions of such companies."[6]

GPhA and its members understand that the generic and biosimilar industry is dependent upon the development of new therapies, which is why a measured approach should be taken to determine the appropriate incentives to spur innovation.

Innovative does not have to mean more expensive, and ensuring that patients have affordable access to innovative treatments is vital. Even the best of medicines are of no value if their high cost puts them out of reach for patients who need them.

We look forward to continuing to work with the Committee on the 21st Century Cures initiative and ensuring that patients have affordable access to life saving medicines.

[6] Testimony of Fred David Ledley, MD, Director, Center for Integration of Science and Industry. Hearing on "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients." (June 11, 2014)

"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients"

United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Statement of
Ann Boynton
Deputy Executive Officer, Benefits Planning and Policy
California Public Employees' Retirement System

June 11, 2014

Chairman Pitts, Ranking Member Pallone, and Members of the Committee, on behalf of the California Public Employees Retirement System (CalPERS), we thank you for convening this hearing to address the critical issue of improving the discovery, development, and delivery of promising new cures to patients and we commend you on your bipartisan effort to address these issues via the "21st Century Cures" initiative. We strongly believe in the need to close any existing gaps between scientific discovery and federal regulation of therapies so that innovation can survive and thrive into the future. CalPERS is pleased to submit testimony for the record to discuss the importance of innovative therapeutic development and our commitment to finding federal policy solutions to support this innovation, while maintaining accessibility and affordability for consumers.

This statement includes a brief overview of CalPERS health programs and benefits, a discussion of our support for federal incentives aimed at driving new drug development and acceleration of approval -- particularly as it relates to biopharmaceuticals -- and our perspective on the need to protect patient access and affordability in the overall pharmaceutical market.

Background on CalPERS

CalPERS was established by state law in 1932 to provide retirement benefits for California public sector employees. In 1962, state law authorized CalPERS to provide health benefits to their members. Our mission is to advance the financial and health security for all who participate in the system.

In 2012, CalPERS spent over $7 billion for health care benefits for over 1.3 million active members, retirees, and their families, including almost $1.5 billion for prescription drugs, or 21 percent of total health care spending. CalPERS prides itself on ensuring access to safe, effective, and affordable prescription drugs, including generic medications. In 2012, CalPERS spent nearly $400 million on generic drugs for its active members, retirees, and their families; and, every year, CalPERS and its members save tens of millions of dollars through the use of safe, effective generic medications.

Biomedical Innovation: Finding Cures for All Patients

Over the past three decades, biomedical research has made historic achievements that have led to new, powerful tools in identifying effective therapies to treat well-known diseases such as cancer, heart disease, and diabetes. Breakthroughs in academic research – much of it federally funded -- as well as a strong biopharmaceutical industry and balanced government regulation has positioned the U.S. as the leader in biomedical innovation. CalPERS is proud to be a partner in accelerating these important scientific breakthroughs while ensuring an appropriate balance between innovation, access, and affordability of critical therapies.

That said, much remains to be done. Despite historic breakthroughs in scientific research, clinical trials, and new, life-saving therapies, many common diseases remain incurable. Heart disease and stroke continue to be leading causes of mortality, psychiatric diseases are serious burden on patients, their families, and society as a whole, and infectious disease presents new, critical challenges in terms of drug-resistance. On top of this, a full 96 percent of orphan diseases remain incurable. These incurable diseases present a "cost" to patients which includes a lack of therapeutic effectiveness as well as a significant economic burden. For example, in 2012, CalPERS spent more than $83 million on just three biologics used to treat rheumatoid arthritis.

In 2012, the President's Council of Advisors on Science and Technology (PCAST), the advisory group made up of the nation's leading scientists and engineers who directly advise the President, set an important goal to "Double the current annual output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and government working together to double the efficiency of drug development, by decreasing clinical failure, clinical trial costs, time to market, and regulatory uncertainty." CalPERS supports this important goal and is proud to continue to be a partner in supporting efforts to increase federal funding to both further scientific research and bring critical medicines to market.

Balancing Innovation with Access and Affordability

As we continue to support scientific research and an accelerated process to bring breakthrough drugs to market, we must also be mindful of the ability for consumers to access and afford essential medications. Overall, breakthroughs in biomedical research and the pace of scientific research have not always led to a significant increase in access to medicines for our employees and retirees. The critical tool to ensure affordability of brand name prescription drugs is timely competition from cost-effective generic alternatives.

The passage of the Drug Price Competition and Patent Term Restoration Act of 1984 provided an important tool for brand name drug companies to recoup costs incurred from research and development for new medications. Patent protection occurs for 50 percent of the development time of a certain drug and 100 percent of the time a drug is under review at FDA. The market exclusivity period for brand drugs is five years. CalPERS believes that the exclusivity period established under current law is appropriate to properly incent innovation while still ensuring generic competition in the marketplace.

Furthermore, many of the most innovative, life-saving therapies available and in development today are in the biopharmaceutical marketplace, known as biologics. However, the significant cost burden of these medications has a measurable, negative impact on consumers and purchasers, including CalPERS. Between 2004 and 2011, the percent of CalPERS participants utilizing specialty medications increased by 33 percent; and, specialty drugs comprised 1.2 percent of drugs dispensed yet represented 17 percent of CalPERS total drug spend. A full 94 percent of CalPERS' specialty drug spending is associated with biologics. CalPERS' total spending for specialty drugs exceeded $250 million in 2011, a 43 percent increase since 2007, and a 120 percent increase since 2004.

The Affordable Care Act (ACA), signed into law by President Obama in March 2010, contained an important provision establishing an abbreviated pathway for biological products that are demonstrated to be "biosimilar" to, or "interchangeable" with, an FDA-licensed biological product. As a result of the passage of the ACA, innovator products were granted a period of at least 12 years of exclusivity on the market before patents may be challenged. We believe that 12 years is more than a sufficient amount of time to allow innovator companies to recoup their investments in research, development and marketing and would not support an extension to the exclusivity period in the law. The FDA is currently establishing standards for the licensing of these products and CalPERS is pleased to be a collaborator and partner as FDA develops policy on this important issue.

Conclusion

Mr. Chairman, CalPERS applauds the efforts of this committee and of Chairman Upton and Congressman DeGette to highlight the issue of innovation. CalPERS supports a balanced approach to creating strong incentives for pharmaceutical innovation and ensuring appropriate access and affordability of medications for consumers. In so doing, we strongly believe the current market incentives under federal law that allow for appropriate multi-year exclusivity and patent protection should be maintained. We look forward to continuing to partner with the public and private sector to ensure that consumers have timely access to safe, innovative and affordable medications.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
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July 1, 2014

Mr. Marc M. Boutin
Executive Vice President and
Chief Operating Officer
National Health Council
1730 M Street, N.W., Suite 500
Washington, D.C. 20036

Dear Mr. Boutin:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Marc Boutin, JD, Executive Vice President and Chief Operating Officer of the National Health Council

Responses to Additional Questions and Member Requests for the Record for the June 11, 2014, 21st Century Cures Initiative Hearing, House Committee on Energy and Commerce

The Honorable Michael C. Burgess

Question: Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative, cutting edge technology that improves the lives of patients?

Advanced and innovative diagnostic tests, including companion diagnostics (class III medical devices), have the potential to dramatically increase the efficacy and safety of medicines by better predicting how patients will respond to a given therapy. These innovative, cutting-edge technologies improve the lives of patients by identifying which patients will benefit from a medicine, and therefore should receive that treatment, and which patients will not benefit or are more likely to suffer side effects of a medicine, and therefore should not receive that treatment. Unfortunately, manufacturers of diagnostic tests have increasingly struggled with the uncertainty surrounding coding and reimbursement of these tests. Open questions include whether these tests would be covered and reimbursed at all, and, if so, would they be reimbursed at a rate that allowed the manufacturer to recoup its investment. This uncertainty makes it difficult for manufacturers to obtain financing and increases the risk of developing these cutting edge technologies. Without increased certainty regarding a test's potential return on investment, some diagnostics may not be developed at all, never making it to patients to help guide their treatment and enhance their clinical outcomes.

Congress recently took a great step forward in addressing the problems with coding and reimbursement of these tests. On April 1 of this year, as part of the Protecting Access to Medicare Act of 2014 (H.R. 4302), Congress enacted provisions that will incentivize the development of innovative diagnostics. These provisions were originally included in H.R. 3116, the Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network Cures Act of 2013, or the MODDERN Cures Act. The new law establishes a value-based payment system for diagnostic tests and a process for assignment of a temporary reimbursement code to a new test after it is approved by the Food and Drug Administration (FDA). I commend Congress for taking this step and believe that this new law will help alleviate some of the coding and reimbursement challenges faced by diagnostic manufacturers, bringing more certainty to the industry and more benefit to patients.

Longer term, the patient community is urging the diagnostics and medical device industries to work with us to develop a framework for integrating patient perspectives into the product development process. Such a framework should create a consensus-based definition for patient engagement, validate methods of engagements for use at each step of the development timeline, and remove unnecessary barriers that currently prevent companies from engaging with patients. We believe this will help alleviate some of the uncertainty faced by manufacturers for coverage and reimbursement of their products by supporting the development of diagnostics tests and medical devices that can demonstrate higher value. The National Health Council is working with other organizations such as the Medical Device Innovation Consortium to create an environment that makes patient engagement a core function of the research, development, and regulatory processes.

The Honorable Henry A. Waxman

Member Request: Would you please provide the committee with the data and information to show whether there are significant numbers of dormant therapies that are waiting to be developed? Would you also please provide the data that explains why 15 years of exclusivity and patent protection are necessary for these therapies?

As Senator Hatch explained in his recent foreword to the *William Mitchell Law Review* issue on the anniversary of the Hatch-Waxman Act: While "the foundation laid by the Hatch-Waxman Act thirty years ago will continue to be the mechanism by which the government incentivizes development of lifesaving drugs. . .we cannot rest on the laurels of this legislative achievement. . .[W]e have an obligation to periodically reevaluate how the balance can be adjusted to account for the sweeping changes in the broader health care sector."[1]

The time has come to reevaluate this balance as current incentives are no longer optimal to incentive new treatments for unmet medical needs. The National Health Council's discussions with individual patient advocacy organizations and drug manufacturers have confirmed to us that manufacturers factor in questions of patent protection when deciding whether or not to continue the development of a drug, particularly for those disease areas in which the clinical development timeline can be long. In addition, I have been told by researchers funded by the National Institutes of Health that much of their most promising research cannot obtain sufficient patent protection to be picked up and developed by a manufacturer – one of the reasons that scientific discoveries fail to translate into clinical benefit for patients. In fact, one 2012 article estimated

[1] Hatch, O. William Mitchell Law Review. Accessible at: http://www.wmitchell.edu/lawreview/Volume40/40_IV.html. (last accessed June 7, 2014)

that roughly 30,000 drugs were abandoned by the pharmaceutical industry over the past thirty years.[2]

The patentability standards of novel and nonobvious explain many situations in which a promising medicine lacks patent protection.[3] An invention is only eligible for a patent if it is new (novel) and it would not have been obvious to make the invention based on the body of knowledge that was already known at the time of its creation (nonobvious). Often, patents protecting potential new drugs will address a family of related drugs, sometimes hundreds of drugs, but only protect a few of the described potential drugs. The fact that the issued patent (which is public) describes the potential drugs renders those drugs unpatentable because they are no longer "new." In addition, other public disclosures (inadvertent or not) can have the same effect, preventing the manufacturer from obtaining a patent protecting a potential drug. Other times the issued patent does protect all the potential drugs described, but the patent expired while the manufacturer was developing one or a few of these drugs, leaving no patent protection for the drugs that are developed later. In addition, in the case of drugs, "obvious" ones are those "that would have been reasonably expected to succeed at the time of their invention . . . drugs that initially look most likely to be effective are often the least likely to be patentable."[4]

We can do better to incentivize and bring treatments to patients suffering from unmet medical needs. For a promising product with no or uncertain patent protection, sufficient protection from generic competition for a specific period of time after FDA approval creates certainty for manufacturers. This would allow them to pursue medicines that have the greatest

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[2]Wadman, Meredith, New Cures Sought from Old Drugs, Nature 490, 15, October 4, 2012.
[3] See in general, Roin, Benjamin N., Unpatentable Drugs and the Standards of Patentability (February 2009). *Texas Law Review*, Vol. 87, pp. 503-570, 2009. Available at SSRN: http://ssrn.com/abstract=1127742
[4] Roin, Benjamin N., Unpatentable Drugs and the Standards of Patentability (February 2009). *Texas Law Review*, Vol. 87, pp. 503-570, 2009. Available at SSRN: http://ssrn.com/abstract=1127742

potential to meet an unmet medical need, even if the treatment has insufficient patent protection. As I mentioned in my written testimony submitted to the Committee on June 11, 2014, the uncertainty created by the reliance on patents discourages companies from pursuing medicines with long development timelines – those intended to prevent disease or treat early stage or chronic diseases – in favor of those with shorter development timelines – those intended to treat later-stage diseases and acute conditions.[5]

In cancer, for example, this leads to more research and development of drugs intended to treat later-stage cancers, reducing the development of promising drugs intended to prevent cancer or treat early-stage disease.[6] Research and development in the later cancer stages is encouraged at the expense of the enormous public health benefit of studying drugs to treat early-stage patients or to prevent cancer. Longer development timelines are also likely for an innovative drug that could treat a disease that has never had any treatments, a drug with a new mechanism of action, or a drug to prevent, cure, or slow the progression of a disease or disability.

The MODDERN Cures Act aligns incentives with the needs of patients by setting a term of regulatory exclusivity for these medicines. We defer to Congress in determining the appropriate length of the exclusivity period, as Congress is uniquely positioned to weigh competing interests and decide on an appropriate balance that reflects the current patent, regulatory, and commercialization realities for manufacturers of new medicines to treat unmet medical needs. We anticipate that passage of the MODDERN Cures Act, with a certain regulatory exclusivity protection period, will result in increased research and development into

[5] Budish et al. National Bureau of Economic Research. Do fixed patent terms distort innovation? Evidence from cancer clinical trials. September 5, 2013. Available at: http://www.nber.org/papers/w19430.pdf. (last accessed June 9, 2014)
[6] Budish et al. National Bureau of Economic Research. Do fixed patent terms distort innovation? Evidence from cancer clinical trials. September 5, 2013. Available at: http://www.nber.org/papers/w19430.pdf. (last accessed June 9, 2014)

medicines with the potential to prevent disease or disability, treat early-stage conditions, and address chronic conditions with long development timelines, such as Alzheimer's disease or other progressive conditions.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 1, 2014

Dr. Samuel E. Gandy
Chair
Alzheimer's Disease Research Center
Mount Sinai Health System
One Gustave L. Levy Place
New York, NY 10029

Dear Dr. Gandy:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

Questions for the Record
Subcommittee on Health
Hearing Entitled:
"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."
June 11, 2014

Responses from Dr. Samuel E. Gandy
Chair, Alzheimer's Disease Research Center
Mount Sinai Health System
Submitted July 16, 2014

The Honorable Michael C. Burgess
Question: Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative and cutting edge technology that improves the lives of patients?

Response: Due to my field of expertise, I can really only speak to neurological conditions and there is little current evidence that would lead one to anticipate the proposal of a Class III medical device for the treatment of Alzheimer's disease. The Class III category is assigned when there is high risk (e.g. neurosurgical implantation of electrodes from which external electrical stimulation [small shocks] can be administered). In neurological and psychiatric diseases in which these devices have proven promising, there is usually some fairly circumscribed brain region that can be targeted with these small shocks. The closest example is in Parkinson's disease, wherein there is a brain region called the subthalamic nucleus that appears to be *over*active. Now, it might seem counterintuitive to think of stimulating a brain region that is overactive. However, nerve cells constantly alternate between moments of excitation separated by moments of unresponsiveness. The explanation for this is that nerve cells must re-equilibrate after excitation and during this re-equilibration period, they are incapable of being excited. The re-equilibration period permits nerve cells to get ready for the next shock. With just the right timing of shocks from an external source that functions as a sort of pacemaker, nerve cells can be induced to spend more time in those unresponsive, re-equilibration periods. The overactivity caused by the disease is thereby reduced by using shocks to induce nerves to spend more time in the unresponsive state. Alzheimer's disease is different in two ways: (1) there is no obvious area of overactivity; and (2) the brain region involved is massive. The cerebral cortex that is involved in Alzheimer's involves the surface for most of the brain, and therefore is far too large and complex to be managed with shocks, although there are early attempts ongoing. Thus, the major barrier in this instance is really the creation of a Class III medical device that benefits Alzheimer's disease, which at this time seems very unlikely just due to the nature of the disease.

The Honorable Michael C. Burgess

Question: When innovative therapies are FDA approved, there is a significant lag time between FDA approval and Medicare coverage decisions leaving these products to be reviewed and paid on a case by case basis. Many of these initial claims will be adjudicated through the Medicare appeals process. The three year back log at the Office of Medicare Hearings and Appeals for Administrative Law Judge hearings creates a financial disincentive for hospitals and providers to use these therapies given the uncertainty regarding timely reimbursement. Would you explain how this severe backlog would impact your hospital's ability to use cutting edge therapies when the reimbursement landscape for Medicare patients is uncertain?

Response: This OMHA backlog is a tremendous problem, and there is no obvious, "one-size-fits-all" solution. The most recent examples were in the several imaging agents developed for visualizing the type of Alzheimer's pathology known as amyloid plaque. Small biotechnology firms (e.g., Avid) and major innovators (e.g., GE) developed radioactive chemicals that were successful as amyloid imaging "ligands" (a name applied to an injected chemical that sticks to some partner molecule in the brain). While CMS was evaluating whether or not to reimburse these ligands, the companies donated ligand to any physician who wanted to prescribe their use in diagnosis. The patient was still responsible for the cost of the nuclear medicine department's time and effort, but the ligand was free. This cut the cost from $4000 under normal circumstances down to $1200 during what was called a "voucher" phase (the vouchers were the documents that physicians used to prescribe these cost-discounted scans). In its initial ruling, CMS declined to reimburse for these tests. The companies, hopeful that this is a temporary state of affairs, continue to offer "vouchers" periodically, wherein ligand is available at no charge, in order to keep the professional and advocacy communities engaged. Based on the initial experience with the negative CMS decision for amyloid imaging, some companies (e.g., GE) discontinued their rush to develop competing ligands and instead have taken the strategy of delaying application for regulatory approval for their new ligands and, in the interim, they will partner with certain medical centers. The companies will provide exclusive access to ligands in exchange for having expert faculty characterize their ligands and work out whether the ligands meet some clinical need. In this way, the case for FDA and/or CMS approval will be strengthened and there will be support from the academic community.

In summary, my first draft response at how to improve the CMS appeals backlog would be for the companies to anticipate the backlog and to be prepared to waive costs for some period of time between FDA registration and CMS approval for reimbursement. This would provide the professional community with a trial period during which they would be able to test the new products for themselves. If the products are truly worthwhile, data from the trial period could be used as evidence during the CMS appeal. This is one example for how industry has responded to the evolving landscape of Alzheimer's diagnosis. In the therapeutic area, pharmaceutical companies have partnered with the NIH for drug testing, especially with the National Institute on Aging's Alzheimer's Disease Cooperative Study (ADCS) Group. The ADCS operates as a national CRO (clinical research organization). By partnering with ADCS, trial results are jointly announced, thereby arriving with the imprimatur of an independent federal-academic body. One would predict that this sort of partnership would reduce the need for OMHA, because drugs would arrive with not just a pharma company's stamp of approval but that of the ADCS (and by

inference, the NIH). Recent partnerships have involved gamma globulin (Gammagard®, Baxter) and solanezumab (Lilly). These examples will not fit all needs arising. More study of CMS applications early in their development is required. In the same way that the FDA encourages pre-IND (investigational new drug) meetings of investigators with the FDA in the trial design phase in order to ensure that the key milestones likely to be required for FDA approval are included in the trial design, perhaps CMS/pharma joint task forces could assess INDs early on in order to identify key milestones likely to be required for CMS approval. While adding an additional review might appear to increase bureaucracy, these "pre-CMS reviews" would almost certainly be less costly less time-consuming than appeals of negative CMS decisions and that would reduce the burden on OMHA. We would encourage any methods that might generate other creative proposals. Perhaps CMS or NIH might hold a national (or international) call for online comment for a 3- to 6-month period so that academics and industry investigators worldwide might contribute ideas on how to solve the OMHA backlog.

The Honorable Cathy McMorris Rodgers

Question: In your testimony, you recommend that Congress develop legislation which provides market exclusivity for orally administered compounds which is independent of their patent life. You put this forward as a solution to one side of the coin-the post-market life of approved therapies. I am certainly open to a discussion on incentives like exclusivity-particularly for therapies where there is a public health need. But I am also curious about what we can do on the other side of the coin the pre-market time period that uses innovation and new science to streamline the approval process and cuts down on the time it takes drugs to get to market. I know you have focused your research on Alzheimer's. Do you have any specific ideas on how we could improve the way we do clinical trials that could help get a breakthrough Alzheimer's drug to market?

Response: First, thank you for your interest in market exclusivity for orally administered compounds for Alzheimer's disease. Your question contains several parts that I will take in turn. With regard to streamlining the process, additional investment in the FDA is one suggestion that comes to mind. The FDA is one bottleneck in the drug approval process, and that agency is pressed from Congress and from advocacy groups to rapidly approve additional drugs. However, faster approval of new drugs without allocation of the resources that agency would require to accelerate its work will increase the risk that a poisonous or worthless drug makes it to market. Such a rushed approval will cause damage: to patients directly; to the government financially; and to the reputation and reliability of the FDA. Another way to streamline the process might involve wider pre-screening of populations in order to generate groups of subjects for trials. The US Preventive Health Service recently advised against this, since we have no effective drugs, a policy that some investigators see as a "Catch 22". Even so, accumulation of pre-screened patients is not the most expensive step. Most individuals show signs of Alzheimer's in their 70s, so if we were able to slow the progress of the disease by 50 percent, most of these individuals would not show symptoms until their 90s. The latest research indicates that our best chance for intervening in Alzheimer's disease may be at the stage of pre-symptomatic prevention, which means initiating treatment in people in their 50s or 60s. However, prevention trials will be much more expensive than the current treatment trials, which, in turn, are already among the most expensive in

medicine. We now require at least 300 subjects and an 18 month trial to conduct treatment trials that can cost around $50 million each. Prevention trials, on the other hand, will require screening of thousands of subjects and will last more than five years, potentially costing $1 Billion in order to move a drug from entry into Phase 1 trials on to the ultimate goal of approval. In order to be approved, a drug must meet certain benefit milestones in at least two independent trials. Given the enormous cost, these trials will be performed serially rather than in parallel. Thus, the newest and most promising innovation in Alzheimer's trials will cause the cost of trials to skyrocket. However, the general consensus is that this is the best next step in terms of research and progression on possible treatments, but the rate of progress will be very slow and very expensive indeed.

The Honorable Cathy McMorris Rodgers

Question: I am aware of ongoing efforts to develop standing Alzheimer's trial sites and robust patient registries as well as efforts to facilitate access to data from unsuccessful trials in a precompetitive manner. What are your thoughts about reforms like these and others? What can we learn from innovative trials in the oncology space to translate into the chronic disease space like Alzheimer's and diabetes?

Response: With regard to standing Alzheimer's trial sites, such a program is maintained by the NIA's Alzheimer's Disease Cooperative Study Group (ADCS), mentioned above in another context. However, the ADCS subject group, in general, already suffer from the symptoms of Alzheimer's disease. Based on what we know about the cause of Alzheimer's and the likely need for presymptomatic intervention, we will indeed require robust registries of people in their 50s and 60s who are willing to commit to long-term prevention trials. Several efforts along this line have been initiated (e.g., the UCSF-Lumosity collaboration on an online brain health registry from which subjects can be recruited for trials). These are low cost strategies for assembling the group of subjects for a trial (called a cohort). However, the expensive part of the trials comes first in the development of the drug and then in reimbursing the physician and staff time and effort involved in periodic assessment. An important part of Alzheimer's clinical trials involves serial neuroimaging studies. The technology here has improved enormously over the past 25 years but the tests cost in the range of $1000- $4000 per exam per patient per visit. The administration of the two serial prevention trials required to gain approval for one new drug could cost as much as $1 Billion. So, while assembling the proper subject cohort is key to running a successful trial, this is by no means the limiting step. The cost of running the trial is limiting.

We agree completely that reports of failed trials should be freely accessible to academic and industry investigators. We certainly cannot afford to make the same mistake over and over. A number of coalitions have been formed wherein major pharmaceutical companies open their shelves to academic medical centers seeking to test drugs that they are not actively pursuing for one reason or another, often because these drugs have failed in some way. In turn, there are major academic efforts at identifying which of these medicines can be repurposed. This is an important collaborative, precompetitive effort. However, as your question implies, we need to know the completely histories of these drugs, including how they have been used in trials and why they have been abandoned.

One key basis for recent successes in oncology has involved a technique known as pharmacogenomics wherein a patient's tumor is studied genetically in order to identify the particular Achilles' heel of that person's tumor. We have had this sort of success at Mount Sinai (http://www.esquire.com/features/patient-zero-1213), and we are now applying the lessons learned from cancer to brain diseases such as Alzheimer's (http://www.mountsinai.org/patient-care/service-areas/neurology/news/nih-grant-to-support-mount-sinai-research-program-to-create-biological-network-model-of-alzheimers-disease-in-partnership-with-new-york-stem-cell-foundation). A limitation is that in cancer one can usually sample the diseased tissue from a living individual, and this is not practical in brain diseases. However, with the sequencing of the human genome, we can often find subgroups of subjects who respond to drugs, but when the responders are mixed together with the nonresponders, the benefit is diluted out and lost. This means that drugs potentially useful for a responder subgroup will be discarded, often leaving behind no record of the promise that it might have held. An example in Alzheimer's disease can be found in the 1% of subjects in whom we think we know the cause because we have identified powerful genes in certain families. Pharma has typically excluded these subjects out of concern that any successful drug might be labeled as exclusively approved for genetic Alzheimer's disease. The NIA has taken up the cause of these rare forms of Alzheimer's and is co-sponsoring prevention trials known as DIAN (Dominantly Inherited Alzheimer's Network) and API (Alzheimer's Prevention Initiative).

The Honorable Cathy McMorris Rodgers

Question: How can we improve our existing research structure in a way which incentivizes more investment? What is the possibility for clinical trials networks? Or more partnerships with NIH? How about the interaction of the SBIR-STTR program with N IH?

Response: In my testimony, I spoke about the need to create an exclusivity policy for orally administered compounds that can slow Alzheimer's. Most of the drugs that are being studied now are biologics, which means they require refrigeration and administration by infusion. In addition to the challenges of maintaining and delivering biologics beyond university and urban centers, their cost will not bend the dementia care cost curve. In fact, a biologic drug treatment for Alzheimer's could increase the cost of care over 20-fold. If that drug were used to prevent Alzheimer's disease, the cost could increase the current Alzheimer's care expenditure by 50-fold or more.

This extended patent life proposal is aimed at incentivizing the pipeline at all levels. The issue of clinical trial networks was covered in the answer to an earlier question about standing clinical trial sites. Over the past 40 years, the NIH has created a number of nationwide networks of centers aimed at characterizing Alzheimer's patients with clinical and imaging methods and enrolling them into a limited number of trials. This patient network already exists, but there is room for enormous expansion. The trial unit is called the Alzheimer's Disease Cooperative Study Group (ADCS), and they operate only a handful of *treatment* trials in parallel at any one moment. What does not exist are assembled cohorts of subjects in their 50s or 60s who are ready, willing, and qualified to participate in *prevention* trials.

Overall, federal investment in Alzheimer's research is disproportionally meager and needs to be improved. Annual NIH funding for Alzheimer's is around 500 million dollars while that for HIV/AIDS and cancer are in the billions of dollars. The number of affected Americans is far greater for Alzheimer's than for the others. Therefore, the number of dollars invested in Alzheimer's research per American affected is $85 vs $2,818 invested in HIV/AIDS research per patient, or $4,411 invested in cancer research per patient affected. Expanding of the SBIR-STTR program would certainly be welcome and would offset some of the void left by the vacation of venture capital (VC) funding from the Alzheimer's space (as attested during the hearing by the heads of two major VC firms). The SBIR-STTR mechanism can help offset the loss of VC dollars. However, that still would not touch the big ticket item: the cost that we need to offset is the $1 Billion that we project will cost a drug company to move an Alzheimer's drug from Phase 1 through to approval. As you well know, Congress has stepped in before to provide market incentives for research (i.e., the Orphan Drug Act and the biologics provision in the Affordable Care Act). This created an explosion in orphan drug research. We need an incentive of this magnitude in the Alzheimer's research space.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
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Majority (202) 225-2927
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July 1, 2014

Mr. Alexis Borisy
Partner
Third Rock Ventures
29 Newbury Street
Boston, MA 02116

Dear Mr. Borisy:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

July 18, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts:

Thank you again for the opportunity to testify before the Subcommittee on Health on the "21st Century Cures: Examining the Role of Incentive in Advancing Treatments and Cures for Patients." As a follow up to your request, below are my responses to the questions asked by several members of the committee.

The Honorable Joseph R. Pitts

1. **The size and cost of clinical trials is an impediment to investment and innovation, particularly for products treating diseases that impact large patient populations. How can advances in technology make trials more efficient?**

   There are advances in technology on multiple fronts that could serve to improve how we can more efficiently and effectively conduct clinical trials. In the 21st century we must move away from the more for more's sake mentality to a philosophy that considers what is actually informative. It is also important to understand that we have already moved into a life-cycle approach to drug development that includes many post-approval monitoring and data collection activities that have not yet been integrated to how we develop, review and approve new medicines. I will briefly discuss 3 areas where modern technologies could serve to improve the development and approval processes.

   Improving FDA Acceptance of Modern Drug Development Tools
   As I discussed in my testimony the ability to utilize modern drug development tools such as biomarkers, patient reported outcomes, and novel clinical trial designs is inconsistent across review divisions. While we have seen significant progress for drugs that treat oncology and rare diseases, we have not seen the same progress in the utilization of modern approaches for chronic and progressive diseases. In the absence of concentrated efforts by regulators to communicate how, when and on what basis modern approaches will be accepted the regulatory process will continue to lag behind modern science. The question is not always what technology is available but rather will the technology that is available be able to be utilized during the regulatory process.

   This issue must be addressed in both a prospective and retrospective manner. On the prospective side there should be a process for sponsors to interact with FDA early in the clinical development process to discuss the use of novel tools and approaches in a clinical development program. Any process should ensure that industry, FDA, and any appropriate external medical experts or patient voices necessary to ensure a fully informed discussion are incorporated into the process. On the retrospective side there needs to be a more consistent and transparent process whereby FDA evaluates biomarkers and modern approaches that are novel or have

been utilized for approval of rare diseases or drugs that treat serious and life-threatening diseases are evaluated via a public commenting process and present ideas on how those tools could be employed in other disease areas to the public. This type of process should also be forward leaning and allow for input regarding modern approaches that are being developed and studied by NIH and other public private partnerships. It is imperative that these activities do not end with a report but rather lead to activities such as adaptive/Bayesian clinical trial methodology development, pilot programs and new guidance. And finally, it is critical that there is a concentrated effort to assess, evaluate and communicate how these approaches could be utilized for drugs that are designed to treat large patient populations.

FDA, should also be looking to work with NIH and public-private partnerships to pilot and establish guidelines for the use of modern tools such as the utilization of smart phones that could improve the ability of sponsors to more effectively obtain patient reported outcomes.

Use of 'Big Data' and Post-Market Real-World Data

The other technological advancement is the ability to collect data from multiple sources. It would be beneficial for Congress to encourage or authorize FDA to accept data from non-traditional sources such as historical data, data from electronic health records, claims databases, registries or other sources to support clinical development activities. We should also consider how these databases could be utilized to empower more effective and efficient clinical development and approval of new medicines. This could include approaches that allow for more reasonably sized pre-market clinical studies on safety and effectiveness with mandatory post-market real-world data collection and analysis to assess the safety and efficacy further in the real-world. Enabling the use of rapidly growing digital health information could greatly advance how we develop new medicines and would serve to attract investment in more disease areas such as cardiology, endocrinology and progressive/chronic neurological diseases.

Adaptive and Expedited Approval Pathways

We have already discussed biomarkers and novel clinical trial designs and their potential to modernize clinical development. We are also making advancements in the ability to develop and utilize diagnostics to identify targeted subpopulations of patients. Improving the process by which FDA approves the utilization of companion diagnostics in drug development could significantly improve the industry's ability to develop medicines for diseases that treat chronic and progressive diseases where there are varying risk-benefit profiles within each disease or where there are genetic markers that may be predictive of how patients may respond to treatments.

There are also adaptive and expedited approval pathways currently being discussed that could enable more investment in and development of medicines for diseases that affect large and diverse patient populations. These include ideas such as Special Medical Use and Adaptive Licensing. The idea is to allow for a prospective clinical development program that is designed to initially evaluate, test and approve a medicine for a subpopulation of patients. The industry sponsor can then conduct subsequent clinical trials to evaluate, test and approve that same medicine for a broader patient population. The European Medical Agency (EMA) is currently conducting a pilot program with selected companies to explore how adaptive licensing can be developed for specific medicines. If authorized in the United States, these types of programs would serve to incentivize investment for drugs designed to treat chronic/progressive diseases.

2. **Understanding that lengthy clinical trials with a large number of participants are currently the norm for drugs treating chronic diseases such as heart diseases and stroke, what processes does FDA in place to provide the necessary certainty to sponsors up front so that, when resources are devoted to drug-development in these areas, investors and companies can plan accordingly? [Please see response to Question 1.]**

In addition to the comments made above, you question as to sponsor confidence in clinical trial development and evaluation by the FDA is not consistent across FDA review divisions. While there have been improvements since passage of FDASIA there is still a need to encourage more scientific dialogue between FDA and sponsors throughout the development process. There are tools such as Special Protocol Assessments (SPA) that are intended to address the issues you raised however these are not used by a majority of sponsors and those that do utilize them often have to undergo a lengthy process to obtain a SPA and does not always offer guarantees that the agreement will be upheld. Thus, many companies make the determination that the value versus the burden leads to a decision to forego utilization of a SPA. That said, in all cases, more scientific interaction with FDA review teams and review divisions should be encouraged to ensure that each drug development team is communicating with the sponsor, external experts as needed and patients as appropriate to ensure that the program is being tested an evaluated in a manner that is reflective of current science, current technologies, and takes into account the disease and patient being treated.

The Honorable Michael C. Burgess

1. **Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative cutting edge technology that improves the lives of patients?**

Securing coverage and payment for Class III medical devices is a very complex and unpredictable process and can add an additional three to five years more before patients can benefit from a new product. Each phase of reimbursement process has its own set of challenges. One of the biggest challenges companies face is the data requirements payors (both government and private) impose before granting coverage because the requirements are often unclear and so high. Also, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it, while physicians and hospitals will not agree to use the product unless they get paid. Equally challenging is that data and utilization requirements are very ambiguous. There is also increasing evidence that payors are raising the standard for coverage determinations.

The Honorable Cathy McMorris Rodgers

1. **Your testimony specially references the length of clinical trials as being an impediment to investment. What are some specific ideas on what we could do to streamline the way trials are conducted? How would this affect investment in the bio-pharma space? Please see response to The Honorable Joseph R. Pitts Question 1.**

2. **How can we improve our existing research structure in a way which incentivizes more investment? What is the possibility for clinical trial networks? Or more partnerships with NIH? How about interaction of the SBIR/STTR program with NIH?**

I serve on BIO's Emerging Companies Section Governing Board. Recently, Reps. Jim Gerlach (R-PA), Richard Neal (D-MA), Mike Kelly (R-PA), and Ron Kind (D- WI) introduced H.R. 4855, the Partnerships to Advance Revolutionary Technology and Novel Entrepreneurial Research (PARTNER) Act. This bill would allow small companies to partner with their investors on a research project and share the tax assets (net operating losses and R&D credits) generated by the R&D that could substantially incentivize investment in the early-stage and clinical development in the biopharmaceutical industry.

It could also be worthwhile to examine current public-private partnerships and examine ideas for creating incentives for increased private sector funding in such endeavors. Partnerships including pre-competitive information sharing among NIH, FDA, academia and industry as well as partnership among medical product developers have and could yield enormous benefits. These types of partnerships can work together to tackle issues such as finding solutions to critical scientific barrier questions and the collection and analysis of things like natural history studies data. All of which can serve to de-risk clinical development and thus make investment more attractive. NIH could also serve a critical role in working with FDA and industry to evaluate, test and validate new approaches to clinical trial development (ex. adaptive clinical trial designs, novel endpoints etc.). Improving the regulatory process for clinical development would serve to incentivize investment in the development of new medicines.

The NIH SBIR/STTR program serves a critical role in providing funding for early-stage proof of concept studies. This program serves to advance research projects to the point where it can attract venture capital. This program has been very successful. However, the investment environment for early-stage research is still a difficult one. As I mentioned in my testimony first-time financings are down 35% from 2008. It may be worthwhile for Congress to consider creating tax incentives for investment in early stage research projects.

Establishing a stable and enduring clinical network infrastructure in the U.S. could considerably reduce costs associated with the start-up, enrollment, investigator training, and site certification for clinical trials. There are currently some clinical trial networks in place such as the Cancer Cooperative Groups funded by the National Cancer Institute. Congress could authorize the establishment of such groups, with consultation between NIH and FDA with funding from government sources and/or public-private partnerships or on a fee-for-service basis.

3. **You mention the need for FDA to allow for the utilization of modern tools- such as biomarkers and personalized medicine to diagnostically define subsets of a disease. Do you think the FDA and its current regulatory framework is equipped to approve these types of products? Do you think there are adequate incentives in the market for these types of innovative diagnostics?**

The current regulatory process for acceptance of modern tools and approaches to clinical development remains inconsistent across review divisions. There appears to be a much stronger willingness to accept modern tools, novel endpoints and flexible clinical trial designs in the oncology and rare disease space but reluctance in other disease areas especially for drugs designed to treat chronic/progressive diseases. Additionally, the criteria by which FDA will

accept novel tools and approaches is often not clearly understood by investors or the industry. As discussed under Question 1, it would be beneficial if the FDA and industry sponsor could interact with FDA early in the clinical development process to discuss the use of novel tools and approaches in a clinical development program. Any process should ensure that industry, FDA, and any appropriate external medical experts or patient voices necessary to ensure a fully informed discussion are incorporated into the process. Additionally, there needs to be a more consistent and transparent process whereby FDA evaluates biomarkers and modern approaches that are novel or have been utilized for approval of rare diseases or drugs that treat serious and life-threatening diseases are evaluated via a public commenting process and present ideas on how those tools could be employed in other disease areas to the public. This type of process should also be forward leaning and allow for input regarding modern approaches that are being developed and studied by NIH and other public private partnerships. It is imperative that these activities do not end with a report but rather lead to activities such as adaptive/Bayesian clinical trial methodology development, pilot programs and new guidance. And finally, it is critical that there is a concentrated effort to assess, evaluate and communicate how these approaches could be utilized for drugs that are designed to treat large patient populations.

There are not, currently, enough incentives to fund activities for the identification of new biomarkers, to develop evidence supporting the utilization of current biomarkers, to develop and conduct novel clinical trials designs or to develop novel diagnostics. The development of novel diagnostics has barriers on multiple fronts.

First, the regulatory process for the inclusion of diagnostics in drug development is often burdensome and communication between review divisions and centers can often be inconsistent and/or cause delays in the clinical programs. One element of the Breakthrough Therapy Designation program is to integrate and coordinate cross-disciplinary review staff early, often and throughout the clinical development program. These activities could be monitored and utilized to establish best practices for how to more effectively review companion diagnostics in general.

Second, reimbursement for diagnostics, while improved after passage of the *Improving Medicare Polices for Clinical Diagnostic Laboratory Tests* in 2014, it is still considered a negative factor when considering whether to invest in the development of novel diagnostics. In my testimony I proposed that the Committee consider a process whereby CMS create a program for diseases important to the public health with high unmet diagnostic needs (ex. Alzheimer's and diabetes) and establish a payment policy for some meaningful determined period of time that would incentivize investment in and development of novel diagnostics for these critical diseases.

Clear payment polices of personalize medicine tools and modern regulatory approaches would advance personalized medicine by leaps and bounds.

The Honorable Gus Bilirakis

1. **Your testimony mentioned that FDA allows for the use of novel endpoints, biomarkers and non-traditional clinical trial designs, but lacks transparency and consistency in their approach. How could we improve the process and encourage regulatory to use every tool in their proverbial toolbox? Please see response to The Honorable Joseph R. Pitts Question 1.**

2. **One mechanism drug companies have to improve certainty about the agency's acceptance of certain clinical trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the agency always held up its end of the binding contract?**

   BIO conducted a survey in late 2013 and found that only 26 % of survey participants have utilized a SPA. Among those that had 78% had to go through multiple submissions and review creating delays in the clinical development program. There is also growing concern that these agreements are not always upheld so it may not be worth the time and effort required to reach an agreement with FDA on a SPA. While there are times where a significant scientific finding would require that a SPA not be upheld we should examine how to improve the SPA process to ensure communication occurs throughout the clinical program under SPA to enable sponsors to adjust if necessary in a manner that minimizes delays and duplicative activities and best enables the program to advance if appropriate.

3. **What barriers are currently in place that limit that potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?**

   As discussed in Question 1, integrating approval requirements with post-market approval requirements would incentivize efforts to collect real-world evidence in a more robust manner. FDA should be working with industry, physicians, patient organizations and other stakeholders to develop methodologies and/or criteria for the utilization of real-world data from sources such as clinical trial registries, electronic health care records and claims databases to conduct virtual clinical trials in the post-approval setting. This could serve to enable approval based on reasonable clinical trial sizes that maintain FDA's gold standard for safety and efficacy and also ensure that information continues to be collected that will allow for analysis and refinement of risk/benefit profiles in the real world.

4. **In your testimony, you touch on the need for certainty after approval and the challenge of ensuring that there is coverage of a new drug or device by Medicare, Medicaid or private insurance. Typically, commercial insurers cover something that Medicare covers. What are the challenges that are faced getting covered and reimbursed under Medicare?**

   One of the biggest challenges with reimbursement for medical devices is the data requirements payors (both government and private) impose before granting coverage because the requirements are often unclear and so high. Also, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it, while physicians and hospitals will not agree to use the product unless they get paid. Equally challenging is that data and utilization requirements are very ambiguous. There is also increasing evidence that payors are raising the standard for coverage determinations.

   With regard to molecular diagnostic tests, there exists considerable uncertainty regarding both the standards for coverage by CMS, and also the amount of payment provided for covered tests. Recently, Congress passed the Protecting Access to Medicare Act of 2014, which created a new, market-based system for pricing molecular diagnostic tests. Although this legislation is a substantial step forward towards recognizing the value that these tests provide the healthcare

system, there are many issues in this legislation that must be interpreted and resolved by CMS to ensure adequate appropriate payment amounts are met. I encourage the committee to remain abreast of the developments in implementing this legislation, and responsive to stakeholders that raise issues as they arise over the next couple of years.

Even if this new system creates an adequate and appropriate payment amount that recognizes the value of molecular diagnostics, the standards of evidence by which these tests are covered by CMS remain unclear. Under the relevant statute, CMS must cover products and services that are "reasonable and necessary" to the treatment of Medicare beneficiaries. This results in broad discretion to CMS to set the evidentiary standards for the products and services they choose to cover, which typically occurs via third party contractors. This results in a system with multiple contractors setting independent coverage policies in different regions of the country, and the standards for evidence required for coverage are not uniform. Further complicating the coverage issue for investors and test developers, CMS lacks adequate transparency regarding the standards used and the rationale of why particular coverage decisions are made. In many cases, CMS and its contractors demand levels and amounts of evidence that a diagnostic business model simply cannot consistently provide. Indeed, the markets for diagnostic tests are many times much smaller than those for therapeutic interventions.

The lack of certainty regarding payment and coverage for molecular diagnostic tests disincentives investors from entering this market. If investors to not have a reasonably clear picture regarding what milestones the test developer must hit to see a return on investment, they are likely to look to other markets. It is critical that CMS better define evidentiary standards that recognize the value that molecular diagnostics provide to the healthcare system, create clear and attainable metrics for achieving coverage, and increase transparency into the rationale for individual coverage decisions.

5. You mentioned that in Europe they have something called the adaptive licensing pilot program and that could help modernize our regulatory system. Would you talk more about this program and how it could be used in the United States?

In March, 2014 the European Medicine Agency (EMA) announced its "adaptive licensing pilot project," an initiative intended to grant earlier access to medicines meant to treat unmet needs. EMA's adaptive licensing framework calls for the authorization of medicines for restricted (i.e. niche) patient populations followed by "iterative phases" of approval. The agency stated that, "The approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients, with the need to provide adequate evolving information on their benefits and risks." The EMA has also postulated that earlier approvals would support subsequent (*i.e.* broader) approvals by allowing sponsors to collect real-world use data, EMA postulated.

In June, 2014 the EMA announced that they have selected two drugs to enter into the pilot program. There are at least 11 drug applications still under consideration. The agency stated it will contact the sponsors of the selected applications to explore how adaptive licensing can be developed for these specific medicines, with input from multiple stakeholders including health technology assessment (HTA) bodies and patient organizations.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has also been engaging

in information gathering activities undertaken to inform the development of their own adaptive licensing pilot program.

This type of pathway has the potential to incentivize investment, especially in drugs that treat chronic/progressive diseases. Congress should consider directing FDA to establish a similar pilot program.

Again, thank you for the opportunity to testify and please let me know if I can provide any additional information.

Sincerely,

Alexis Borisy
Partner
Third Rock Ventures

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
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July 1, 2014

Mr. Mike Carusi
General Partner
Advanced Technology Ventures
485 Ramona Street
Palo Alto, CA 94301

Dear Mr. Carusi:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

July 16, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts:

Thank you again for the opportunity to testify before the Subcommittee on Health on the "21st Century Cures: Examining the Role of Incentive in Advancing Treatments and Cures for Patients." As a follow up to your request, below are my responses to the questions asked by several members of the committee.

The Honorable Joseph R. Pitts

1. **The size and cost of clinical trials is an impediment to investment and innovation, particularly for products treating diseases that impact large patient populations. How can advances in technology make trials more efficient?**

   In-line with the significant advancements made in computer science and information technology, computational modeling and simulation have positively impacted device development and reduced the time to verify and validate the performance of breakthrough technologies. Such methods also have potential to revolutionize the field with regards to clinical trials, but have not been leveraged to their full potential due to historical perspectives and regulatory requirements related to animal and human studies. Leveraging technological advances and modeling will not only allow new ideas to be tested with greater confidence and decreased cost, but will also allow medical device clinical trials to be conducted while reducing risk to patients.

2. **Understanding that lengthy clinical trials with a large number of participants are currently the norm for drugs treating chronic diseases such as heart disease and stroke, what processes does FDA have in place to provide the necessary certainty to sponsors up front so that, when resources are devoted to drug development in these areas, investors and companies can plan accordingly?**

   As a reminder, my area of focus/expertise is more medical device focused than drug focused. With that said, I believe the question holds true for medical device clinical trials addressing chronic diseases as well. If a sponsor successfully meets the endpoints of an FDA approved clinical trial (via the IDE process), it is essential that the FDA remain true to its word and approve the product. Moving goal posts will prevent manufacturers from pursuing such studies if there remains uncertainty on approval even if the agreed upon endpoints are met. Progress has been made in this area and the FDASIA bill is expected to help. With that said, it remains essential that these obligations are met.

   Additionally, I would reference back to your first question. Solutions to improve clinical trial efficiency are likely to be most impactful in the areas of chronic disease. Post-marketing studies can also play a role in this area as well.

3. **To date, CMS has declined to provide guidance regarding the extent to which changes may be made to a durable medical equipment (DME) product such that it remains a "modified" or "upgraded" product subject to the grandfathering provision of the three-year minimum lifetime requirement (MLR) for DME, and not a "new" product that may no longer be eligible for reimbursement as DME. What is the impact of this lack of guidance on Medicare beneficiary access to innovative medical devices?**

   The fact that medical device manufacturers cannot make any reasonable inferences regarding whether modifications or upgrades to their existing DME products will push these products outside the DME benefit is a significant threat to Medicare beneficiary access to the best medical technologies. Medical device development is an iterative process whereby products are continually assessed for potential improvements for the benefit of patient health and experience – and for opportunities to reduce healthcare costs. The current lack of guidance on the application of the grandfathering provision of the three-year MLR for DME seriously stifles innovation of medical devices, which detrimentally affects Medicare beneficiary access to the most advanced medical technologies. More specifically, It is believed that the limited guidance CMS has chosen to provide has discouraged manufacturers from investing in medical innovation. Even with the agency's proposed clarification to the grandfathering provision of the three-year MLR, it is believed that manufacturers will not be allowed to introduce technological advancements to their products without the threat of losing Medicare coverage.

4. **What are your recommendations for DME reimbursement policy regarding the application of the grandfathering provision of the three-year MLR that continues to promote and foster innovation of medical devices?**

   CMS should consider avoiding a "one-size fits all" policy regarding the grandfathering provision that fails to recognize the wide and complex array of DME products covered by the three-year MLR. The proposed grandfathering policy should be applied in a way that would allow continued Medicare coverage of "modified" products as DME even though they may continue to have an expected life of less than three years (as was historically the case before the products were modified). It is suggested that CMS convene a study panel to examine at a minimum the following central questions:

   - Must a "modified" item fall within the same HCPCS code and/or DME product category as a grandfathered item in order for it to also fall within the grandfathering provision?

   - Would a premarket approval (PMA) product approved after January 1, 2012 that is similar in structure and function to grandfathered products be considered a "modified" version of the grandfathered products? Is a newly-cleared 510(k) product considered to be a "modified" version of a predicate device?

   - What modifications can be made to a grandfathered product (including products with disposable components) that would result in more efficient and effective treatments (and thereby improve the health of Medicare beneficiaries) but reduce the minimum lifetime of the product?

   In short, it is recommended that CMS, in its continued implementation of the three-year MLR, instead promote policies that create incentives for manufacturers to make innovative modifications

to medical devices that will improve the health of Medicare beneficiaries and thereby lower costs to the Medicare program.

The Honorable Michael C. Burgess

1. **Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative cutting edge technology that improves the lives of patients?**

While the unpredictability of the FDA has been of primary concern in recent years, we are now most concerned with the risk presented by ensuring a new technology will be covered and paid for, both by public and private insurers. Securing coverage and payment for Class III medical devices is a very complex and unpredictable process and can add an additional three to five years more before patients can benefit from a new product. This issue is, in part, due to the difference in statutory missions of FDA and CMS – being that FDA requires demonstrated safety and effectiveness, while CMS needs assurance that the new technology is reasonable and necessary for beneficiaries, resulting in the need for additional and expensive human trials. However, in recent years, increased difficulty in achieving coverage by public and private insurers for new medical devices and diagnostics has been observed.

Historically, medical device manufacturers have been able to leverage FDA sponsored clinical trials for submission to payers (CMS and private payors) to gain reimbursement for innovative products. This, however, no longer appears to be the case. There is increasing evidence that payors are raising the standard for coverage determinations. One study by Tufts University researchers found that the probability a therapy considered for national coverage under the Medicare program will be approved dropped by more than 60 percent between 1999 and 2007. When coverage was granted, the scope was more limited than the indications approved by the FDA in 40 percent of the cases studied.[1] While Medicare national coverage determinations represent a relatively limited universe, we are finding that both private payors and government programs are increasing the bar for coverage and reimbursement decisions. What is most troubling is that it is often not clear where that bar lies.

The overall process of obtaining coverage and reimbursement represents a classic "chicken and the egg" dilemma for the investment community. On the one hand, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it. On the other, physicians and hospitals will not agree to use the product unless they get paid. Equally challenging, the data and utilization requirements these organizations require for approval are ambiguous at best. They are unwilling to commit in advance to reimburse a product downstream if clearly defined endpoints are met. It becomes a never-ending process fraught with risk and uncertainty.

Given these challenges, we need to make the coverage process in both the public and private payor context more open and transparent. We need to take steps to expedite coverage and reimbursement decisions. We need to foster improved collaboration among the innovator, payor and patient communities. And we need to ensure that our government programs are more receptive to rapid coding and coverage of new technologies. Specific recommendations can be found in my testimony.

The solution is not to move back from appropriate incentives to provide high value care or to suggest that products that do not offer therapeutic benefits should be covered; rather it is to make the public policy changes necessary to assure that the new emphasis on cost does not result in the unintended and unwanted consequence of undermining development and adoption of new and better treatments.

The Honorable Cathy McMorris Rodgers

1. **Would you explain the evaluation that a VC does of a medical device start-up? Are looking at how promising the idea is, what the outlook is for FDA approval, whether or not CMS will cover the device, or a combination of factors? How has this continuum changed over the last 10-15 years?**

   Venture capitalists make investment decisions in medical device start-ups based upon our level of confidence that we can generate a meaningful return on the investment for our investors (i.e., Limited Partners). To generate a meaningful return, the dollars out (from an exit) must be more than the dollars in (from our investment). This also must occur within a reasonable period of time (4-6 years) and with a reasonable probability of success (30% - 40% of our companies historically fail/do not return capital).

   As such, venture capitalists evaluate the factors that affect the nature of the exit (i.e., timing, size, and M&A or IPO), the level of investment, and the probability of success. Factors affecting the nature of the exit include the level of unmet clinical need, the strength of the team, market size, strategic relevance, strength of intellectual property, level of competition, and likely inflection point when an IPO or acquisition will occur. Factors affecting the level of investment include technical complexity, clinical complexity, regulatory path, reimbursement path, commercialization path and again the strength of the team. Lastly, factors affecting risk often touch on each of the elements noted above (i.e., what is the likelihood our assumptions will prove true). As venture capitalists, we are willing to take risk on one or two key items but we tend to shy away from opportunities that have multiple or compounded risks.

   Over the past 10-15 years, the dollars required to build a medical device company have grown considerably (now >$100 million) while the dollars received at the time of exit have remained steady or actually fallen. Similarly, timelines have lengthened (now 8-10 years) and the probability of success has fallen (now 50% - 60% of our companies will fail/not return capital). All of these factors result in an investment profile where the "math" no longer works and the sector is no longer an attractive investment opportunity for our investors.

   The reasons for this decline are varied, but at its core, it can be attributed to four main factors: 1) increased timelines and data requirements by FDA, 2) increased timelines and data requirements by CMS and private payers, 3) increased regulatory requirements, and 4) an unfavorable tax environment. As discussed in my testimony, progress has been made with FDA (although our work is by no means complete). We now need to make progress in the other areas as well.

The Honorable Gus Bilirakis

1. **Your testimony mentioned that FDA allows for the use of novel endpoints, biomarkers and non-traditional clinical trial designs, but lacks transparency and consistency in their approach. How**

can we improve the process and encourage regulators to use every tool in their proverbial toolbox?

I believe this point actually relates more to drug clinical development and is likely to be better addressed by Alexis Borisy (who also testified). My area of focus/expertise tends to be more medical device focused.

2. **One mechanism drug companies have to improve certainty about the agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the agency always held up its end of the binding contract?**

   Once again, this point relates to drug clinical development and is likely better addressed by Alexis Borisy from Third Rock Ventures.

3. **What barriers are currently in place that limit the potential of using clinical and outcomes data to learn about how therapies are working on patients in the real world? How should we address them?**

   I don't have an answer to this question at this time.

4. **In your testimony, you touch on the need for certainty after approval and the challenge of ensuring that there is coverage of a new drug or device by Medicare, Medicaid or private insurance. Typically, commercial insurers cover something that Medicare covers. Would you talk about some of the challenges that are faced getting covered and reimbursed under Medicare?**

   See Question 1 from the Honorable Michael C. Burgess.

Thank you again for your leadership on this important initiative and please let me know if I can provide you with any additional information.

Sincerely,

Mike Carusi
General Partner
Advanced Technology Partners

[1] Chambers J.D., Morris S, Neumann P, and Buxton M. (March 2012) Factors Predicting Medicare National Coverage: An Empirical Analysis. *Medical Care Journal*, 50(3).

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 1, 2014

Dr. Steven B. Miller
Senior Vice President and
Chief Medical Officer
Express Scripts Holding Company
One Express Way
St. Louis, MO 63121

Dear Dr. Miller:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

EXPRESS SCRIPTS®

July 16, 2014

The Honorable Joseph Pitts
Chairman, Subcommittee on Health
U.S. House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts:

Thank you for the opportunity to testify before the Subcommittee on Health at the hearing entitled, "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients." Getting incentives "right" will be crucial if the United States wants to continue to foster innovation while controlling health care costs.

I am pleased to respond to the three questions posed by Representative Ed Whitfield.

1. The data correlating patient choice to improved adherence and compliance is a national issue of huge importance. Patients who fail to take their medication as prescribed have higher healthcare costs. They often suffer from unnecessary complications, including heart attacks, strokes, heart failure, amputations, end-stage renal disease and vision loss. Express Scripts estimates that failure to take medications as prescribed costs the U.S. approximately $317 billion annually[i,ii,iii]. Several studies document the association between adherence and positive clinical outcomes (e.g., high blood pressure, glucose levels for diabetes) for several medical conditions.[iv,v,vi,vii,viii] Express Scripts research demonstrates that switching a patients' diabetes medication from a 30-day retail fill to a 90-day mail order pharmacy fill improves adherence, leading to lower all-cause and diabetes-related healthcare costs.[ix] Previous studies have also indicated that medication adherence is associated with reducing disease morbidity,[x] reducing healthcare resource utilization,[xi] and decreasing hospitalization.[xii] The Centers for Medicaid and Medicare Services (CMS) has understandably adopted goals to increase adherence as part of their Medicare Star Ratings clinical metrics. This new metric reinforces that better outcomes and cost containment can be achieved through improved medication adherence.

2. We do view the opportunities to improve health outcomes and lower costs being driven by taking a more holistic approach across the entire medical community. PBMs can and do play a critical role in this process. The pharmacy benefit is the most frequently utilized health care benefit. Pharmacy data is real time and powerful. Appropriate use of pharmacy represents the sharp end of the spear when it comes to improving patients' outcomes and reducing costs. If we can use every touch point with a patient to both educate and activate their good intentions, we are more likely to have a good outcome.

At Express Scripts, we have designed a system in which we use behavioral approaches combined with our clinical specialization to engage patients, activate good intentions, close gaps in care and share data with the other provider partners. This holistic approach has the potential to truly move the health of our country in a new direction.

3. The GAIN Act as enacted by Congress provides incentives to promote the development of novel antibiotics to treat unmet medical needs. In addition to this law, science continues to evolve and prior investments in basic research like the human genome project are now making a difference. It is our belief that investment in basic research via the NIH is still the best approach to spurring innovation and developing treatments for unmet medical needs. As we stated in our testimony, incentives can often have perverse effects and actually stifle innovation as seen with periods of exclusivity for pharmaceuticals. If incentives are to be utilized, they should be very narrowly defined, time limited and treated as pilots. Otherwise, they could potentially add substantially to long term health care costs.

Again, thank you for the opportunity to testify before the Committee. I appreciate the Committee's attention to this important topic.

Sincerely,

Steven B. Miller
Senior Vice President and Chief Medical Officer
Express Scripts Holding Company

[i] Nasseh K, et al. Cost of Medication Nonadherence Associated with Diabetes, Hypertension, and Dyslipidemia. Amer Journal of Pharmacy Benefits. 2012;4(2):e41-e47.

[ii] New England Healthcare Institute (NEHI). Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. Available at:

http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed January 19, 2012.

[iii] Balkrishnan R. The importance of medication adherence in improving chronic disease-related outcomes: what we know and what we need to know further. *Med Care*. 2005;43(5):517-520.

[5] Bramley TJ, Gerbino PR, Nightenqale BS, Frech-tamas F. "Relationship of Blood Pressure Control to Adherence With Antihypertensive Monotherapy in 13 Managed Care Organizations" (J Manag Care Pharm. 2006;12(3):239-45)

[6] Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. The impact of Adherence with osteoporosis therapy on fracture rates in actual practice (Osteoporosis Int (2004) 15:1003-1008

[vi] Ho MP, Sperrus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, Krumholz HM, Rumsfeld JS. "Impact of Medication Therapy Discontinuation on Mortality After Myocardial Infarction" (Arch Intern Med 2006;166;1842-1847)

[vii] Pladevall M, Williams LK, Potta LA, Divine G, Xi H, Lafata J Diabetes Care "Clinical Outcomes and Adherence to Medication Measured by Claims Data in Patients with Diabetes" 2004 (Diabetes Care 27:2800-2805)

[viii] Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata J, Ownby DR, Johnson CC. "Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma." (J Allergy Clin Immunol. 2004 Dec;114(6):1288-93)

[ix] Devine, S., Vlahiotis, A., & Sundar, H. (2010). A comparison of diabetes medication adherence and healthcare costs in patients using mail order pharmacy and retail pharmacy. *Journal of Medical Economics*,*13*(2), 203-11.

[x] Albert NM. Improving medication adherence in chronic cardiovascular disease. *Crit Care Nurse*. 2008;28(5):54-64.

[xi] Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and health care cost. *Med Care*. 2005;43(6):521-530.

[xii] Stuart BC, Simoni-Wastila L, Zhao L, Lloyd JT, Doshi JA. Increased persistency in medication use by U.S. Medicare beneficiaries with diabetes is associated with lower hospitalization rates and cost savings. *Diabetes Care*. 2009;32(4):647-649.

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COMMITTEE ON ENERGY AND COMMERCE

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July 1, 2014

Dr. Fred D. Ledley
Professor
Center for Integration of Science and Industry
Jennison 110 Bentley University
175 Forest Street
Waltham, MA 02452

Dear Dr. Ledley:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

BENTLEY
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July 7, 2014

The Honorable Joseph R. Pitts
Chairman, Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Congressman Pitts:

Thank you for the opportunity to appear before the Subcommittee on Health on Wednesday, June 11, 2014 to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

I have received your letter dated July 1, 2014 and the additional question presented by Congressman Burgess. I hereby submit my formal response for the hearing record.

The Honorable Michael C. Burgess

Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative cutting edge technology that improves the lives of patients?

This question is outside of my area of expertise and I am unfamiliar with the issue raised.

Sincerely,

Fred Ledley, M.D.
Professor, Department of Natural & Applied Sciences, Management
Director, Center for Integration of Science and Industry
Bentley University,
Waltham, MA 02452
Tel: 781.891.2046
Email: fledley@bentley.edu

Cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 1, 2014

Mr. C. Scott Hemphill
Professor of Law
Columbia Law School
435 West 116th Street
New York, NY 10027

Dear Mr. Hemphill:

Thank you for appearing before the Subcommittee on Health on Wednesday, June 11, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Wednesday, July 16, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Response to Questions for the Record

C. Scott Hemphill
Professor of Law
Columbia Law School

House Committee on Energy and Commerce
Subcommittee on Health

Hearing on 21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients

July 16, 2014

Question #1

Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative cutting edge technology that improves the lives of patients?

Response

I have no comment in response to this question, as I have not examined the Class III medical device market or regulatory regime.

Question #2

In your testimony, you mentioned the evergreening provision. I understand that is not just a one-time event, but could go on forever wherever a small change can produce another 15 years of exclusivity. Mr. Boutin claims in his testimony that MODDERN Cures has the strongest anti-evergreening language ever included in legislation. Do you agree with that? Do you think that the law prevents evergreening or could companies get multiple 15 years exclusivity?

Response

The MODDERN Cures Act is vulnerable to evergreening strategies in two ways. The first problem is that a branded firm can earn multiple 15-year exclusivity periods under the Act, provided it develops or acquires a second drug that contains a new "active moiety." For example, a second drug treating the same disease in the same class as the first would be eligible for a fresh exclusivity period, if it contains an active ingredient with a slightly different chemical structure. (For biologics, the active moiety in the second drug must not be "highly similar," an undefined term that is vulnerable to evasion.)

Moreover, in certain circumstances, the second drug may be eligible for exclusivity even if the active ingredient has been previously approved. This potential scenario arises when a branded firm develops a so-called single enantiomer of a previously approved drug. For example, Prilosec is a mixture of two enantiomers, only one of which is therapeutically effective. Nexium is in essence a purified version of Prilosec, containing only the single useful enantiomer.

Under the Act, the developer of a drug like Nexium is likely to argue that the single enantiomer is a distinct "active moiety" eligible for a second 15-year period. The FDA might be expected to disagree, as the agency rejected a similar interpretation of its rule governing five-year new chemical entity (NCE) exclusivity.[1] On the other hand, a branded firm might respond that the definition contained in the NCE rule does not mention enantiomers, and in other contexts the FDA has treated a single enantiomer as a distinct active moiety.[2]

"Active moiety" is undefined in the Act, leaving the scope of protection uncertain. Branded firms would have a strong incentive to pursue an expansive interpretation of the term. The result could be large and disproportionate extensions of branded drug exclusivity, unjustified by the limited incremental benefit to patients incentivized by such extensions.

The second problem is product hopping. Near the end of the 15-year exclusivity period, the branded firm has an incentive to shift patients to a second, related drug, prior to generic entry. As discussed in my testimony, this shift can be accomplished by promoting the new product, increasing the relative price of the old product, or withdrawing the old product from the market. The product-hopping problem is not unique to the MODDERN Cures Act, but rather endemic to the regulatory regime governing generic entry.

However, the MODDERN Cures Act would worsen the product-hopping problem by lengthening the base period of protection that is extended by the switch. As a consequence, the 15-year exclusivity period would serve as a floor on the duration of protection, rather than a ceiling. In addition, the two evergreening techniques might be deployed in tandem, if a branded firm used product-hopping to shift patients from one drug with exclusivity to a second drug with exclusivity. The potential result would be an effective 30-year term of protection.

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[1] See 54 Fed. Reg. 28,872, 28,898 (1989) (preamble to rule); 59 Fed. Reg. 50,338, 50,359 (1994) (reaffirming rule). A recent statutory change permits an approved enantiomer to receive NCE exclusivity under certain limited circumstances.

[2] See 21 C.F.R. § 314.108(a) (defining "active moiety" for purposes of FDA rule implementing NCE exclusivity); FDA, Approved Active Moieties to Which FDA Has Issued a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050002.htm (listing Prilosec (omeprazole) and Nexium (esomeprazole) as distinct "active moiet[ies]" for which pediatric studies have been requested).

○